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(54) **MDC proteins and DNAs encoding the same.**

(57) The present invention provide a gene present in a commonly deleted region of a chromosome in breast and ovarian cancers and encoding a novel protein, the protein ("MDC protein") encoded by the gene, a method for the diagnosis of cancer by using an antibody combinable to the protein, and others.

A detailed genetic map of human chromosome 17 was constructed to analyze the chromosome in breast and ovarian cancer tissues, and a gene encoding a novel protein was cloned and its structure was determined. As a result of gene analysis using DNA probes derived from the gene, a gene mutation was confirmed in breast cancer tissues. Moreover, a transformant carrying a plasmid containing the gene was grown to obtain the MDC protein. Furthermore, a monoclonal antibody was prepared by using the protein as antigen.

EP 0 633 268 A2

Background of the Invention

Field of the Invention

5 The present invention relates to MDC proteins, DNAs encoding the same, and gene analysis methods using the DNAs. The present invention can be utilized in such fields as medical treatment and diagnosis.

Description of the Related Art

10 The opinion that mutations in cellular proteins play an important role in the onset of cancer has been known for long. Recent advancement in genetic engineering enables analysis of gene mutations in tumor cells, and has brought about a marked progress in the field of cancer research.

Up to this time, the analysis and identification of oncogenes have made such progress that the number thereof has amounted to several tens. On the other hand, attention has been focused on tumor suppressor
15 genes for these several years. The tumor suppressor genes which have been discovered thus far include the Rb gene for retinoblastoma (Friend, S.H. et al., Proc. Natl. Acad. Sci. USA, 84, 9095, 1987), the p53 gene (Lane, D.P. et al., Nature, 278, 261, 1979) and the APC gene (Kenneth, W.K. et al., Science, 253, 661, 1991) for colorectal tumor, the WT1 gene for Wilms' tumor (Call, K.M. et al., Cell, 60, 509, 1990), and the like. In the case of the p53 gene, some families are known to be inheriting mutations in the gene ["Li-
20 Fraumeni syndrome" (Makin, D. et al., Science, 250, 1233, 1990; Srivastava, S. et al., Nature, 348, 747, 1990)]. Moreover, it is becoming increasingly clear that defects in multiple genes, and not in a single gene, contribute to the progression of the malignant phenotype of cancer, and it is believed that there exist much more unidentified oncogenes and tumor suppressor genes. The discovery and elucidation of them are expected by not only investigators and clinicians, but also common people in all the world.

25 Breast cancer is classified into hereditary (familial) breast cancer and nonhereditary (sporadic) breast cancer, and hereditary breast cancer is classified into early-onset and late-onset diseases according to the age of onset. It has been revealed by linkage analyses that, at least early-onset familial, breast cancer linked to a very small region on chromosome 17 (Hall, J.M. et al., Science, 250, 1684-1689, 1990). Moreover, it has been shown that hereditary ovarian cancer is also linked to the same region (Narod, S.A. et al., Lancet, 338, 82-83, 1991).
30

Accordingly, it is believed that a tumor suppressor gene is present in this region and protein deficiency or mutation induced by an allelic deletion or mutation of the gene is one of the causes of breast and ovarian cancers.

It is believed that in the onset of common (sporadic) breast cancer as well, the occurrence of an
35 acquired mutation or allelic deletion of the gene in this region results in protein mutation or deficiency and this causes the transformation of a normal cell to a breast cancer (Sato et al., Cancer Res., 51, 5794-5799, 1991). Consequently, isolation of the causative gene present in this region and identification of the protein encoded by the gene are expected as an urgent problem to not only physicians and investigators in all the world, but also common people, particularly women in Europe and America where there are numerous
40 patients with breast cancer.

The present invention provides novel proteins involved in breast and ovarian cancers, DNAs encoding them, and methods for the testing and diagnosis of cancer by using them.

The present inventors disclose a novel gene encoding a 524-amino acid protein which was isolated
45 from chromosomal region 17q21.3 where a tumor suppressor gene(s) for breast and ovarian cancers is thought to be present (Nature genetics, 5, 151-157, 1993; this paper is referred in Nature genetics, 5, No. 2, 101-102, 1993).

Disclosure of the Invention

50 Brief Description of the Drawings

Fig. 1 is a diagram showing the positions on chromosome 17 to which 342 cosmid clones hybridize. Clone names are designated by clone numbers alone.

Fig. 2 is a diagram showing partial deletions on chromosome 17q in ovarian cancers. Solid circles
55 represent the loss of heterozygosity (LOH) and open circles represent the retention of both alleles. Two commonly deleted regions are designated by sidelines.

Fig. 3 is a diagram showing partial deletions on chromosome 17q in breast cancers. Solid circles represent the loss of heterozygosity (LOH) and open circles represent the retention of both alleles. Two

commonly deleted regions are designated by sidelines.

Fig. 4 is a diagram showing the process starting with markers on chromosome 17q21.3 and leading to the isolation of the gene, as well as the regions where genomic rearrangements occurred in tumor tissues (hatched boxes). Clone names are designated by clone numbers alone.

5 Figs. 5-7 are diagrams showing the detection of genomic rearrangements in breast cancers by Southern-blot analysis. Symbols N and T represent DNAs from normal tissue and tumor tissue, respectively.

Fig. 8 is a graph showing a working curve for determining the concentration of the MDC protein by ELISA using a monoclonal antibody and a rabbit polyclonal antibody.

10 Summary of the Invention

The present inventors constructed a multitude of cosmid clones having DNA fragments of human chromosome 17 introduced therein. Then, each of the multitude of cosmid clones was localized
15 throughout the chromosome by fluorescent in-situ hybridization (FISH; Inazawa et al., Genomics, 10, 1075-1078, 1991). The cosmid clones (cosmid markers), localized on the chromosome, enabled construction of a high-resolution physical map of human chromosome 17. The clone names of the cosmids as probes, i.e., the probe names, their detailed map positions and diagrammatical summary of the mapping are shown in Tables 1-3 and Fig. 1, respectively. In Fig. 1, clone names are designated by clone numbers alone.

Table 1

	No.	Probe name	Locus symbol	Chromosomal localization	No.	Probe name	Locus symbol	Chromosomal localization
5	1	cCI17-1		17q21.1	67	cCI17-501		17q21.3
	2	cCI17-7		17q22	68	cCI17-502		17p11.2
	3	cCI17-11		17p11.2	69	cCI17-504		17q24
	4	cCI17-24		17q21.1-q21.2	70	cCI17-505	D17S544	17p12-p11.1
	5	cCI17-25		17q12	71	cCI17-506	D17S545	17q21
	6	cCI17-28		17q21.3	72	cCI17-507		17q21.3
10	7	cCI17-32		17q11.2	73	cCI17-508	D17S546	17q25.1-q25.2
	8	cCI17-35		17q21.3	74	cCI17-509		17q24
	9	cCI17-44		17q23.1	75	cCI17-510		17q23
	10	cCI17-50		17q23.1	76	cCI17-511		17q25.1-q25.2
	11	cCI17-57		17q21	77	cCI17-513	D17S548	17q11.2
	12	cCI17-63		17q21.3	78	cCI17-514		17q25.1
	13	cCI17-90		17q12-q21.1	79	cCI17-515		17q22
15	14	cCI17-95		17q23.1	80	cCI17-516	D17S550	17q25.1
	15	cCI17-96		17q21.3	81	cCI17-517		17q21.3
	16	cCI17-97		17q21.31	82	cCI17-518		17q25.3
	17	cCI17-315	D17S521	17q25.1-q25.2	83	cCI17-519	D17S551	17q25.2-q25.3
	18	cCI17-316		17q12-q21.1	84	cCI17-520		17q11.2
	19	cCI17-317		17q11.2	85	cCI17-521		17q25.1-q25.2
	20	cCI17-321		Centromere	86	cCI17-523		17q22
20	21	cCI17-403		17q21.2-q21.3	87	cCI17-524		17q21.1-q21.2
	22	cCI17-412		17q11.2	88	cCI17-525		17p13.1
	23	cCI17-415		17q21.1-q21.2	89	cCI17-526		17q11.2-q12
	24	cCI17-422		17q22	90	cCI17-527		17q21.3
	25	cCI17-425		17q11.2	91	cCI17-528		17q22
	26	cCI17-428		17q23.1	92	cCI17-529	D17S552	17q25.1-q25.2
	27	cCI17-451		17q21.1-q21.2	93	cCI17-530		17q23
25	28	cCI17-452	D17S524	17q25	94	cCI17-532		17p11.2
	29	cCI17-453	D17S525	17p13	95	cCI17-533		17q21.3
	30	cCI17-454	D17S526	17q23	96	cCI17-535		17q12-q21.1
	31	cCI17-456	D17S527	17q23.1-q23.2	97	cCI17-536		17p11.2
	32	cCI17-457		17q11.2	98	cCI17-539		17q21.3
	33	cCI17-458	D17S528	17q21.1-q21.2	99	cCI17-540		17q25
	34	cCI17-460	D17S529	17q11.2	100	cCI17-541		17q21.3
	35	cCI17-462		17q23	101	cCI17-542		17q21.3
30	36	cCI17-463		17q21	102	cCI17-543		17q11.2-q12
	37	cCI17-464		17q24.3-q25.1	103	cCI17-544		17q25.1
	38	cCI17-465	D17S531	17q25.1-q25.2	104	cCI17-545		17q25.1
	39	cCI17-466		17q25.1-q25.2	105	cCI17-546		17q24.3-q25.1
	40	cCI17-467		17q25	106	cCI17-547		17q21.3
	41	cCI17-468	D17S532	17q11.2	107	cCI17-548		17q23
	42	cCI17-469	D17S533	17q25.2-q25.3	108	cCI17-549		17q25.3
35	43	cCI17-471		17p13.3-p13.2	109	cCI17-550		17q23
	44	cCI17-473	D17S534	17q11.2	110	cCI17-551		17q25.1-q25.2
	45	cCI17-475	D17S535	17q11.2	111	cCI17-552		17q12
	46	cCI17-477		17q21.3	112	cCI17-553		17q23
	47	cCI17-479		17q21.3	113	cCI17-554		17q25.1
	48	cCI17-480		17q25.1-q25.2	114	cCI17-557		17q25.1-q25.2
	49	cCI17-482	D17S536	17q11.2	115	cCI17-559		17q24.3-q25.1
40	50	cCI17-483		17p13	116	cCI17-560		17q25.1-q25.2
	51	cCI17-484	D17S537	17p13.1	117	cCI17-561		17q25
	52	cCI17-485		17q12	118	cCI17-562		17q11.2
	53	cCI17-486		17q25.1	119	cCI17-563		17q25.1
	54	cCI17-487	D17S538	17q25.1	120	cCI17-564		17q25.1
	55	cCI17-488	D17S539	17p13.2-p13.1	121	cCI17-565		17q23
	56	cCI17-489	D17S540	17q23	122	cCI17-567		17q21.3
	57	cCI17-490		17q11.2	123	cCI17-568		17q25
45	58	cCI17-491		17p13.1	124	cCI17-569		17q12
	59	cCI17-492	D17S542	17q11.2	125	cCI17-570		17q11.1
	60	cCI17-493		17q25.1-q25.2	126	cCI17-571		17p13
	61	cCI17-494		17q22	127	cCI17-572		17q25.1
	62	cCI17-495		17q25	128	cCI17-573		17q25.3
	63	cCI17-497		17q11.2	129	cCI17-574		17q12-q21.2
	64	cCI17-498		17p11.2	130	cCI17-576		17q21.1-q21.2
50	65	cCI17-499		17q21.1-q21.2	131	cCI17-577		17q25.1
	66	cCI17-500		17p.12	132	cCI17-578		17q11.2-q12

Table 2

	No.	Probe name	Locus symbol	Chromosomal localization	No.	Probe name	Locus symbol	Chromosomal localization
5	133	cCI17-579		17q25.1	198	cCI17-652		17q22
	134	cCI17-581		17q11.2	199	cCI17-653		17q22
	135	cCI17-582		17q21.3	200	cCI17-654		17p13
	136	cCI17-583		17q12-q21.1	201	cCI17-655		17q23
	137	cCI17-584		17q21.3	202	cCI17-656		17q25.1
	138	cCI17-586		17p13	203	cCI17-657		17p13
10	139	cCI17-587		17p13	204	cCI17-658		17q21.3
	140	cCI17-588		17p13.1	205	cCI17-659		17q25.1
	141	cCI17-590		17q12	206	cCI17-660		17q25.1
	142	cCI17-591		17q24	207	cCI17-662		17p12
	143	cCI17-592		17q21.3	208	cCI17-663		17q25.1
	144	cCI17-593		17q25.1-q25.2	209	cCI17-664		17q25.1-q25.2
	145	cCI17-594		17q25.2-q25.3	210	cCI17-665		17q23
15	146	cCI17-595		17q25.1-q25.2	211	cCI17-666		17q23.1
	147	cCI17-596		17q11.2	212	cCI17-667		17q24
	148	cCI17-597		17q25.3	213	cCI17-668		17q22
	149	cCI17-598		17q12-q21.1	214	cCI17-669		17p13
	150	cCI17-599		17q12	215	cCI17-670		17q21.3
	151	cCI17-600		17q23	216	cCI17-671		17q11.2
	152	cCI17-601		17q21.1-q21.2	217	cCI17-672		17q25.1-q25.2
20	153	cCI17-602		17q11.2-q12	218	cCI17-673		17q12-q21.1
	154	cCI17-603		17p11.2	219	cCI17-674		17q21.3
	155	cCI17-604		17q23	220	cCI17-675		17q21.3
	156	cCI17-605		17q21.1-q21.2	221	cCI17-676		17q23
	157	cCI17-606		17p13	222	cCI17-677		17q12-q21.1
	158	cCI17-607		17q25	223	cCI17-678		17q23
	159	cCI17-608		17p11.2	224	cCI17-679		17q23.1
	160	cCI17-609		17q21.3	225	cCI17-680		17p13
25	161	cCI17-610		17q12-q21.1	226	cCI17-681		17p11.1-p11.2
	162	cCI17-611		17q22	227	cCI17-683		17q11.2
	163	cCI17-612		17q21.3	228	cCI17-684		17q25.1-q25.2
	164	cCI17-613		17q25.1	229	cCI17-685		17p13
	165	cCI17-614		17q21.3	230	cCI17-687		17q12
	166	cCI17-615		17q21.1	231	cCI17-688		17p11.2
	167	cCI17-616		17q25.1	232	cCI17-690		17q11.2-q12
30	168	cCI17-617		17q21.3	233	cCI17-691		17q25.1
	169	cCI17-618		17q23.1	234	cCI17-692		17q23
	170	cCI17-619		17q21.3	235	cCI17-693		17p11.2
	171	cCI17-621		17q25.1-q25.2	236	cCI17-694		17p11.2
	172	cCI17-622		17q12	237	cCI17-695		17p11.2
	173	cCI17-623		17q25.1-q25.2	238	cCI17-696		17q23.3
	174	cCI17-624		17p13	239	cCI17-697		17q25
35	175	cCI17-625		17q23	240	cCI17-698		17q11.2
	176	cCI17-626		17q23	241	cCI17-699		17q23
	177	cCI17-627		17p13	242	cCI17-700		17q23
	178	cCI17-628		17q23	243	cCI17-701		17q21.3
	179	cCI17-630		17q11.2	244	cCI17-702		17q25.2-q25.3
	180	cCI17-631		17p11.2	245	cCI17-703		17p13
	181	cCI17-662		17q22	246	cCI17-704		17q23
40	182	cCI17-633		17q12	247	cCI17-705	D17S554	17p11.2
	183	cCI17-634		17q21.3	248	cCI17-706	D17S555	17q12
	184	cCI17-636		17p13	249	cCI17-707	D17S556	17q25.1-q25.2
	185	cCI17-637		17q12	250	cCI17-708		17p13
	186	cCI17-638		17p11.2	251	cCI17-709		17p12
	187	cCI17-639		17q12	252	cCI17-710	D17S557	17q25.3
	188	cCI17-640		17q11.2	253	cCI17-711		17q32.1
	189	cCI17-641		17q25.1	254	cCI17-712	D17S558	17p11.2
45	190	cCI17-642		17q12-q21.1	255	cCI17-713	D17S559	17p13
	191	cCI17-643		17q21.3	256	cCI17-714	D17S560	17q25.3
	192	cCI17-644		17q23	257	cCI17-715		17q21.3
	193	cCI17-645		17p13	258	cCI17-716	D17S561	17p13
	194	cCI17-646		17p13	259	cCI17-717		17p13
	195	cCI17-647		17q25.1-q25.2	260	cCI17-719		17q25
	196	cCI17-650		17q12	261	cCI17-721		17q23
50	197	cCI17-651		17q25.1	262	cCI17-722	D17S563	17q25.2-q25.3

Table 3

No.	Probe name	Locus symbol	Chromosomal localization	No.	Probe name	Locus symbol	Chromosomal localization
263	cCI17-723		17p13	304	cCI17-834		17q11.2-q12
264	cCI17-724	D17S564	17p11.2	305	cCI17-835		17q21.3
265	cCI17-726		17q25	306	cCI17-841		17p12
266	cCI17-727	D17S566	17p13	307	cCI17-1005		17q21.3
267	cCI17-728	D17S567	17p12	308	cCI17-1008		17q21.3
268	cCI17-729	D17S568	17q11.2	309	cCI17-1016		17q23.1
269	cCI17-730		17q21.3	310	cCI17-1018		17q21.2-21.3
270	cCI17-732	D17S570	17p13.2	311	cCI17-1019		17q23.1
271	cCI17-733		17q25.1	312	cCI17-1024		17q12
272	cCI17-735	D17S572	17q25.3	313	cCI17-1029		17q11.2
273	cCI17-736	D17S573	17q21.3	314	cCI17-1030		17q22
274	cCI17-737	D17S557	17q25.2-q25.3	315	cCI17-1031		17q11.2
275	cCI17-739	D17S575	17q25.1	316	cCI17-1032		17q23.1-23.2
276	cCI17-741		17q25.3	317	cCI17-1049		17q21.3
277	cCI17-742		17q25	318	cCI17-1055		17q21.3
278	cCI17-743		17q23.3	319	cCI17-1059		17q21.1-q21.2
279	cCI17-744		17q23	320	cCI17-1063		17q12
280	cCI17-745	D17S577	17p13	321	cCI17-1073		17q11.2
281	cCI17-801		17q11.2-q12	322	cCI17-1079		17q12
282	cCI17-802		17p11.2	323	cCI17-1082		17q22
283	cCI17-808		17q25.1-q25.2	324	cCI17-1094		17q21.1
284	cCI17-809		17q23	325	cCI17-1101		17q12
285	cCI17-810		17p13.2-p13.1	326	cCI17-1103		17q11.2
286	cCI17-812		17q25.1	327	cCI17-1106		17q11.2
287	cCI17-813		17q23	328	cCI17-1702		17q21.1-q21.2
288	cCI17-814		17p11.2	329	cCI17-1705		17q21.2-q21.3
289	cCI17-815		17q24	330	cCI17-1706		17q21.1-q21.2
290	cCI17-816		17q23	331	cCI17-1707		17q21.2-q21.3
291	cCI17-817		17q23	332	cCI17-1709		17q12
292	cCI17-818		17p11.2	333	cCI17-1710		17q21.3
293	cCI17-820		17q12	334	cCI17-1711		17q12
294	cCI17-821		17p13	335	cCI17-1715		17q12
295	cCI17-822		17q11.1	336	cCI17-1717		17q21.3
296	cCI17-823		17q12	337	cCI17-1719		17q11.2
297	cCI17-825		17p11.2	338	cCI17-1720		17q24.3-q25.1
298	cCI17-826		17q11.2	339	cCI17-1722		17q23
299	cCI17-827		17p11.2	340	cCI17-1723		17q21.3
300	cCI17-828		17p11.2	341	cCI17-1724		17q11.2
301	cCI17-831		17q25.1-q25.2	342	cCI17-1725		17q21.1
302	cCI17-832		17p11.2	343	pCMM86		17q23
303	cCI17-833		17q23				

From among these markers, ones exhibiting restriction fragment length polymorphism (RFLP) in which the lengths of restriction fragments vary with the individual, namely RFLP markers, were selected. The selected marker clones, the restriction enzymes used, and the particular lengths of several fragments detected thereby are shown in Tables 4-6.

Table 4

	No.	Probe name	Locus symbol	Enzyme	Allele size (frequency)	Chromosomal localization
5	2	cCI17-7	D17S860	PvuII	3.0 kb(0.33)	
	16	cCI17-97	D17S861	PstI	1.8+1.2 kb(0.67) 8.2 kb(0.92)	17q21.3
	17	cCI17-315	D17S521	TaqI	4.7+3.5 kb(0.08) 2.0 kb(0.67)	17q25.1-q25.2
10	18	cCI17-316	D17S862	MspI	1.8 kb(0.33) 3.1 kb(0.33)	17q12-q21.1
	19	cCI17-317	D17S522	TaqI	2.6-3.9 kb 4 alleles VNTR, 60% heterozygosity also polymorphic with MspI, PstI, PvuII	17q11.2
	29	cCI17-453	D17S525	BglII	5.8-7.5 kb 4 alleles VNTR, 50% heterozygosity also polymorphic with EcoRI, TaqI, PstI, PvuII, MspI	17p13
15	42	cCI17-469	D17S533	MspI	2.0-2.6 kb 5 alleles VNTR, 83% heterozygosity also polymorphic with EcoRI, TaqI, PvuII	17q25.2-q25.3
	54	cCI17-487	D17S538	EcoRI	5.8 kb(0.75) 3.3 kb(0.25)	17q25.1
20	56	cCI17-489	D17S540	MspI	3.3 kb(0.25) 2.1 kb(0.50)	17q23
				TaqI	1.5 kb(0.50) 1.35 kb(0.50)	
				PvuII	1.2 kb(0.50) 0.7 kb(0.50)	
	58	cCI17-491	D17S863	TaqI	3.6 kb(0.75) 3.3 kb(0.25)	17p13.1
25	59	cCI17-492	D17S542	BglII	2.1 kb(0.40) 1.4 kb(0.60)	17q11.2
	61	cCI17-494	D17S865	EcoRI	10.3 kb(0.92) 7.8 kb(0.008)	
	70	cCI17-505	D17S544	MspI	3.1 kb(0.58) 3.0 kb(0.42)	17p12-p11.1
				TaqI	4.1 kb(0.67) 2.7+1.4 kb(0.33)	
30	71	cCI17-506	D17S545	MspI	3.0 kb(0.33) 2.6 kb(0.67)	17q21
	73	cCI17-508	D17S546	MspI	4.6 kb(0.50) 4.0 kb(0.50)	17q25.1-q25.2
	30	cCI17-516	D17S550	TaqI	4.1 kb(0.25) 2.4+1.7 kb(0.75)	17q25.1
35				PvuII	3.4 kb(0.83) 2.2 kb(0.17)	
	38	cCI17-525	D17S866	MspI	2.7 kb(0.42) 2.3 kb(0.58)	
	113	cCI17-562	D17S587	TaqI	3.5 kb(0.42) 3.2 kb(0.58)	
				PvuII	7.1 kb(0.92) 6.6 kb(0.08)	
40	137	cCI17-584	D17S868	MspI	3.8 kb(0.25) 3.6 kb(0.75)	
	166	cCI17-615	D17S869	PstI	5.2 kb(0.42) 4.7 kb(0.58)	
	243	cCI17-701	D17S870	TaqI	1.7-2.5 kb 6 alleles VNTR, 67% heterozygosity also polymorphic with MspI, PstI, PvuII, RsaI	17q21.3
45	244	cCI17-702	D17S871	MspI	4.1 kb(0.83) 3.4 kb(0.17)	17q25.2-q25.3
				RsaI	5.2 kb(0.83) 4.1 kb(0.17)	
				BglII	6.6 kb(0.83) 5.6 kb(0.17)	
50				PvuII	2.9 kb(0.83) 2.2 kb(0.17)	

Table 5

	No.	Probe name	Locus symbol	Enzyme	Allele size (frequency)	Chromosomal localization
5	245	cCI17-703	D17S877	TaqI	2.6-3.8 kb 4 alleles VNTR, 50% heterozygosity also polymorphic with MspI, RsaI, PstI, PvuII	17p13
	247	cCI17-705	D17S554	PstI	4.3 kb(0.50) 2.3 + 2.0 kb(0.50)	17p11.2
10	250	cCI17-708	D17S878	PvuII	2.6-9.0 kb 10 alleles VNTR, 87% heterozygosity also polymorphic with MspI, TaqI, BglIII, PstI, EcoRI	17p13
	252	cCI17-710	D17S557	MspI	2.0-2.6 kb 5 alleles VNTR, 100% heterozygosity also polymorphic with RsaI, TaqI, PstI, PvuII, EcoRI	17q25.3
	254	cCI17-712	D17S558	MspI	3.1 kb(0.58) 2.9 kb(0.42) 6.6 kb(0.67) 4.3 + 2.3 kb(0.33) 7.1 kb(0.50) 3.9 + 3.2 kb(0.50)	17p11.2
15				TaqI		
	255	cCI17-713	D17S559	MspI	2.2-2.8 kb 3 alleles VNTR, 50% heterozygosity also polymorphic with PstI	17p13
20	256	cCI17-714	D17S560	RsaI	4.5 kb(0.58) 4.3 kb(0.42) 3.8 kb(0.75) 2.8 kb(0.25) 3.8 kb(0.58) 3.5 kb(0.42) 2.6 kb(0.58) 2.4 kb(0.42) 1.5 kb(0.58) 1.4 kb(0.42)	17q25.3
				TaqI		
				BglIII		
25				PvuII		
	257	cCI17-715	D17S872	PstI	3.3 kb(0.17) 3.0 kb(0.83) 3.6 kb(0.87) 3.3 kb(0.13)	17q21.3
				EcoRI		
30	258	cCI17-716	D17S561	TaqI	2.4 kb(0.87) 1.3 + 1.1 kb(0.13)	17p13
	261	cCI17-721	D17S864	RsaI	2.9 kb(0.25) 1.6 kb(0.75) 4.4 kb(0.83) 3.9 kb(0.17)	17q22-q23
				BglIII		
	262	cCI17-722	D17S563	MspI	4.1 kb(0.83) 3.4 kb(0.17) 5.2 kb(0.83) 4.1 kb(0.17) 6.6 kb(0.83) 5.6 kb(0.17) 2.9 kb(0.83) 2.2 kb(0.17) 13.0 kb(0.75) 12.5 kb(0.25)	17q25.2-q25.3
35				RsaI		
				BglIII		
				PvuII		
40				EcoRI		
	263	cCI17-723	D17S873	MspI	3.0 kb(0.33) 1.7 kb(0.67) 0.8 kb(0.70) 0.5 kb(0.30) 3.6 kb(0.33) 1.9 kb(0.67) 5.8 kb(0.50) 5.3 kb(0.50) 4.6 kb(0.58) 4.2 kb(0.42)	17p13
				RsaI		
				TaqI		
45				PstI		
				PvuII		
	266	cCI17-727	D17S566	PvuII	2.6-9.0 kb 10 alleles VNTR, 87% heterozygosity also polymorphic with MspI, TaqI, BglIII, PstI, EcoRI	17p13
50	268	cCI17-729	D17S568	MspI	4.6 kb(0.58) 2.6 kb(0.42)	17q11.2

55

Table 6

No.	Probe name	Locus symbol	Enzyme	Allele size (frequency)	Chromosomal localization
269	cCI17-730	D17S874	MspI	2.2-3.5 kb 4 alleles VNTR, 83% heterozygosity also polymorphic with TaqI, BglII, PstI, PvuII	17q21.3
270	cCI17-732	D17S570	RsaI	3.2 kb(0.50)	17p13.2
			BglII	2.7 kb(0.50)	
				8.5 kb(0.50)	
			PstI	3.2 kb(0.50)	
				2.5 kb(0.58)	
			PvuII	1.7 kb(0.42)	
				4.2 kb(0.50)	
				4.1 kb(0.50)	
271	cCI17-733	D17S875	MspI	3.4 kb(0.75)	17q25.1
				2.6 kb(0.25)	
272	cCI17-735	D17S572	MspI	4.1 kb(0.83)	17q25.3
				3.4 kb(0.17)	
			RsaI	5.2 kb(0.83)	
				4.1 kb(0.17)	
			PvuII	2.9 kb(0.83)	
				2.2 kb(0.17)	
273	cCI17-736	D17S573	TaqI	1.7-2.5 kb 7 alleles VNTR, 100% heterozygosity also polymorphic with MspI, RsaI, PstI, PvuII	17q21.3
275	cCI17-739	D17S575	MspI	3.3 kb(0.33)	17q25.1
				2.4 kb(0.67)	
278	cCI17-743	D17S876	TaqI	4.3 kb(0.17)	
				2.8 kb(0.83)	

RFLP markers are characterized in that they can be used to distinguish between two alleles inherited from parents by the difference in polymorphism ("informative") [however, they are indistinguishable when both of them have the same polymorphic pattern ("not informative")]. If such a difference in polymorphic pattern between two alleles ("heterozygosity") exists in normal tissues and the loss of heterozygosity (LOH) is detected in tumor tissues, this implies the allelic deletion in the RFLP marker site on a specific chromosome of tumor tissues. It is generally believed that the inactivation of tumor suppressor genes on both alleles, as caused by the deletion of one allele and the mutation in the other, may lead to malignant transformation. Thus, it is assumed that a tumor suppressor gene is present in a region commonly deleted in many cancers.

Using the detailed chromosome map and RFLP markers thus obtained, the present inventors examined about 300 breast cancers and about 100 ovarian cancers for LOH in chromosome 17. As a result, it was revealed that, in informative cases, a region (of 2.4 cM) lying between cosmid markers cCI17-701 and cCI17-730 located in the neighborhood of 17q21 was deleted with high frequency.

Fig. 2 shows partial deletions on chromosome 17q in ovarian cancers. Solid circles represent the loss of heterozygosity (LOH) and open circles represent the retention of both alleles. Two commonly deleted regions are designated by sidelines.

Fig. 3 shows partial deletions on chromosome 17q in breast cancers. Solid circles represent the loss of heterozygosity (LOH) and open circles represent the retention of both alleles. Two commonly deleted regions are designated by sidelines.

One of the commonly deleted region partially overlapped with the region in which the presence of a causative gene was suggested by linkage analyses of families affected with hereditary breast cancer. When 650 cases of sporadic breast cancer were examined for somatic rearrangements by Southern-blot analysis using cosmids located to the overlapping region as probes, it was revealed that a partial region in the DNA of cosmid clone cCI17-904, which had been selected as described above, detected amplification. On closer examination of this alterations, it was found that segments each having about 6-9 kb were connected with each other to form an abnormal repetition consisting of about 4-6 copies. Moreover, a gene encoding a novel protein was isolated by screening cDNA (DNA having a complementary base sequence reverse-transcribed from messenger RNA) libraries by using, as probe, a restriction fragment of this cosmid clone having a sequence which was conserved among other species. When the sequence structure of this gene was determined and the presence or absence of genomic alterations of this gene in breast cancers was examined, a distinct gene mutation was identified. These results have revealed that deficiency or mutation

in this protein and the allelic deletion or mutation of the DNA encoding it deeply participate in the onset of breast and ovarian cancers.

Fig. 4 shows the above-described process starting with a group of markers and leading to the isolation of the gene, as well as the regions where genomic rearrangements occurred in tumor tissues. Clone names are designated by clone numbers alone.

The present invention is very important in that it can provide methods and materials for solving difficult problems (such as risk diagnosis, early finding, course watching, determination of a treatment plan, and estimation of prognosis) concerning at least a part of breast and ovarian cancers, for example, by examining the presence or absence of deficiency or mutation in the protein of the present invention or the presence or absence of the allelic deletion or mutation of the gene encoding it, and thereby bring about a marked advance in the technology in this field.

Specifically, the present invention provides (1) an MDC protein which comprises the whole or part of the protein represented by SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3 or SEQ ID NO:4, or which consists of a protein substantially equivalent to one comprising the whole or part of the protein represented by SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3 or SEQ ID NO:4, (2) a DNA which comprises the whole or part of the DNA represented by SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8 or SEQ ID NO:9, or which consists of a DNA substantially equivalent to one comprising the whole or part of the DNA represented by SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8 or SEQ ID NO:9, (3) a plasmid containing the DNA as set forth in the above (2), a transformant carrying the plasmid, i.e., a transformant transformed with the plasmid, and a process for the production of the MDC protein described above, which comprises the steps of culturing the transformant described above and collecting the resulting expression product, (4) an antibody which can bind to the MDC protein described above as an antigen, and (5) a primer, probe or marker which has a DNA sequence comprising a part of the DNA sequence of the DNA as set forth in the above (2), or a DNA sequence complementary to a part of the DNA sequence of the DNA as set forth in the above (2), and a gene analysis method which comprises the step of hybridizing the primer or probe described above to a DNA to be tested.

The term "MDC protein" in this specification means a protein and a peptide (including a oligopeptide and a polypeptide) involved in the definition of the term, "the MDC protein".

Further scope and applicability of the present invention will become apparent from the detailed description given hereinafter. However, it should be understood that the detailed description and specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description. The present invention will be specifically described hereinbelow.

Detailed Description of the Invention

(1) Isolation of cDNA clones

Cosmid clones having a DNA derived from human chromosome 17 introduced therein can be produced, for example, by extracting chromosomal DNA from a human-mouse hybrid cell line containing a single human chromosome 17 in a mouse genomic background, and incorporating fragments of the chromosomal DNA into a vector such as pWEX15, according to a method reported by Tokino et al. (Tokino et al., Am. J. Hum. Genet., 48, 258-268, 1991). From among them, clones having an insert derived from the human chromosome can be selected by colony hybridization using the whole human DNA as probe.

The map position of each of the cosmid clones can be determined by FISH. Then, they can be used as markers to construct a high resolution physical chromosome map. Moreover, RFLP markers can be selected on the basis of the fragment length pattern in southern blot analysis (Nakamura et al., Am. J. Hum. Genet., 43, 854-859, 1988). If this map and these RFLP markers are utilized to examine DNAs obtained from the tumor tissues of cancer patients for LOH (loss of heterozygosity), the commonly deleted region on the chromosome in the tumor tissues can be localized to a very small region near q21 of chromosome 17.

Southern-blot analysis of the DNAs from tumor tissues by using a cosmid clone, whose hybridizable portion is present in this localized region, as probe makes it possible to select clones having a DNA sequence associated with genomic alterations in the tumor tissues. Moreover, Southern-blot analysis of the chromosomal DNAs of various mammals by using restriction fragments of the cosmid clone as probes makes it possible to select a fragment containing a DNA sequence conserved among other species and involved in fundamental cellular functions. DNA sequences encoding important proteins are often conserved among other species. In fact, many of the hitherto isolated genes for hereditary diseases are conserved

among other species (Call, K.M. et al., Cell, 60, 509-520, 1990).

If the DNA fragment thus obtained is used as probe, the cDNA of the gene present in a localized region near q21 of human chromosome 17 can be cloned. The base sequence of this cDNA can be determined by a conventional manner (Maniatis, J. et al., Molecular Cloning 2nd. ed., Cold Spring Harbor Laboratory Press, N.Y. 1989).

In order to confirm that the DNA clones thus obtained are clones of the desired causative gene, their sequences may be used to examine the presence or absence of genomic alterations in cancer patients and the incidence of genomic alterations according to the SSCP method (Orita, M. et al., Genomics, 5, 874-879, 1984; Orita, M. et al., Cell, 60, 509-520, 1990), the RNase protection method (Winter, E., Perucho, M. et al., Proc. Natl. Acad. Sci. USA, 82, 7575-7579, 1985; Myers, R.M. et al., Science, 230, 1242-1246, 1985) and other methods.

(2) Confirmation of the whole structure of the gene

It has been confirmed that the DNA sequences of two cDNAs obtained by the above-described procedure are novel and are those of the DNAs represented by SEQ ID NO:6 and SEQ ID NO:7. The corresponding amino acid sequences have also been identified as those of the proteins represented by SEQ ID NO:2 and SEQ ID NO:3. Moreover, 5'-RACE and RT-PCR have revealed the DNA sequence of the DNA represented by SEQ ID NO:8, and the amino acid sequence of the protein represented by SEQ ID NO:4 has been deduced as one corresponding to the DNA sequence. Furthermore, with regard to genomic DNA, the structure of the DNA represented by SEQ ID NO:9 including introns and exons has been revealed by analyzing the base sequence of the original cosmid clone cCl17-904 and comparing it with the base sequence of the isolated cDNA clone to determine the intron-exon junctions.

By the present inventors, proteins comprising the whole or part of the amino acid sequence of the protein represented by SEQ ID NO:1, which is an amino acid sequence common to all of the above-described proteins, are named MDC proteins and will hereinafter be referred to as MDC proteins.

The term "a part of the protein" means, for example, a polypeptide having or comprising an amino acid sequence consisting of a continuous, at least three amino acids which is described in SEQ ID NO:1. The amino acid sequence consists of preferably at least three to five amino acids, still more preferably at least eight or at least eight to ten amino acids, and most preferably at least eleven to twenty amino acids. It is to be understood that polypeptides each having or comprising an amino acid sequence consisting of a continuous, more than 20 amino acids which is described in SEQ ID NO:1 can also be used.

As used herein, the term "substantially equivalent" means that, in proteins comprising the whole or part of the amino acid sequence of the protein represented by, for example, SEQ ID NO:1, their amino acid sequences are attended with the replacement, deletion and/or insertion of one or more amino acids, but they can produce an equal effect in research and diagnosis using the proteins comprising the whole or part of the amino acid sequence of the protein represented by, for example, SEQ ID NO:1. Such equivalents also fall within the scope of the present invention and also called as MDC proteins.

The DNA sequence common to all DNAs encoding MDC proteins is one of the DNA represented by SEQ ID NO:5.

A DNA in accordance with the present invention can be utilized in gene analysis and diagnosis. That is, a primer or probe comprising a part of the DNA sequence of the DNA according to the present invention, or comprising a DNA sequence complementary to a part of the DNA sequence of the DNA according to the present invention is used in gene analysis and diagnosis.

Part of the DNA sequence consists of at least six bases, preferably at least 8 bases, still more preferably 10-12 bases and particularly preferably about 15-25 bases. That is, the oligonucleotide used as primer or probe comprises at least six bases derived from the DNA sequence of the DNA according to the present invention or derived from the DNA sequence complementary to the DNA sequence of the DNA according to the present invention, and, if necessary, other base(s).

In connection with the DNAs of the present invention, the term "substantially equivalent" has the same meaning as described above for the proteins, except that their base sequences are attended with the replacement, deletion and/or insertion of one or more bases.

The introduction of replacement, deletion and insertion mutations into a particular base sequence can be accomplished according to any of conventional methods including those described in F.M. Ausubel et al., "Current Protocols in Molecular Biology", 1987, Chapter 8.

The MDC protein encoded by the DNA according to the present invention, i.e., the MDC protein according to the present invention, can be utilized by using it as an epitope to prepare an antibody. This antibody can be used in experimental and diagnostic reagents. The term "epitope" means an antigenic

determinant of a polypeptide and is generally composed of at least 5 amino acids. It is well known that a polypeptide composed of 6 amino acids binds with an antibody, as disclosed in, for example, Published Japanese Translation of International Patent Application No. 60-500684.

5 (3) Recombinant expression vectors and transformants generated therewith

A transformant can be obtained by incorporating a DNA encoding human MDC protein, which has been obtained by the above-described procedure, or a fragment thereof into a suitable vector and introducing this vector into suitable host cells. By culturing this transformant with a conventional manner, large amounts of
 10 human MDC protein can be obtained from the culture. More specifically, a recombinant expression vector can be produced by linking a DNA encoding a human MDC protein or a fragment thereof on the downstream side of the promoter of a vector suited for its expression according to a well-known method using restriction enzymes and DNA ligase. Usable vectors include, for example, plasmids pRB322 and pUC18 derived from *Escherichia coli*, plasmid pUB110 derived from *Bacillus subtilis*, plasmid pRB15
 15 derived from yeast, phage vectors λ gt10 and λ gt11, and vector SV40 derived from an animal virus. However, no particular limitation is placed on the type of vector used, so long as it can be replicated and amplified in the host. Similarly, no particular limitation is placed on the promoter and terminator, so long as they are compatible with the host used for the expression of the DNA base sequence encoding the human MDC protein. They may be used in any suitable combination depending on the host. The DNA used can be
 20 any of DNAs encoding human MDC protein. It is not limited to the base sequences represented by SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8 and SEQ ID NO:9, but can be any of DNAs in which a part of the base sequence has undergone replacement, deletion, insertion or a combination thereof, whether intentionally or not. In addition, chemically synthesized DNAs can also be used.

A transformant is generated by introducing the recombinant expression vector thus obtained into a host
 25 according to the competent cell method (J. Mol. Biol., 53, 154, 1970), the protoplast method (Proc. Natl. Acad. Sci. USA, 75, 1929, 1978), the calcium phosphate method (Science, 221, 551, 1983), the in vitro packaging method (Proc. Natl. Acad. Sci. USA, 72, 581, 1975) or the virus vector method (Cell, 37, 1053, 1984). The host used can be *Escherichia coli*, *Bacillus subtilis*, yeast or animal cells, and the resulting transformant is grown in a suitable medium depending on the host. Usually, the transformant is grown at a
 30 temperature of 20 to 45°C and a pH of 5 to 8, optionally with aeration and stirring. Separation and purification of the MDC protein from the culture may be carried out using a suitable combination of well-known separation and purification techniques. These well-known techniques include salting-out, solvent precipitation, dialysis, gel filtration, electrophoresis, ion exchange chromatography, affinity chromatography, reverse-phase high-performance liquid chromatography and the like.

35 (4) Preparation of antibodies

Antibodies can be prepared in the usual manner by using an antigen of which epitope part comprises an MDC protein. For example, a polyclonal antibody can be prepared by fully immunizing an animal such
 40 as mouse, guinea pig and rabbit through a plurality of subcutaneous, intramuscular, intraperitoneal or intravenous injections of the antigen described above, collecting blood from this animal, and separating serum therefrom. Commercially available adjuvants may also be used.

A monoclonal antibody can be prepared, for example, by immunizing a mouse with the antigen described above, fusing its spleen cells with commercially available mouse myeloma cells to produce a
 45 hybridoma, and collecting an antibody from the culture supernatant of the hybridoma or the ascites of a mouse inoculated with the hybridoma.

The MDC protein which is used as antigen or is used to prepare an antigen need not necessarily have the whole amino acid structure described in SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3 or SEQ ID NO:4, but may have a partial structure of the amino acid sequence described in SEQ ID NO:1, SEQ ID NO:2, SEQ
 50 ID NO:3 or SEQ ID NO:4. Alternatively, the MDC protein may be a variant or derivative of the MDC protein represented by SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3 or SEQ ID NO:4. The antigen may be an MDC protein as such, or a fusion peptide consisting of an MDC protein (including peptide) and another peptide. Preparation of the fusion peptide may be carried out according to either biological techniques or chemical synthesis techniques.

55 These antibodies enable identification and determination of the MDC protein present in human biological specimens and can hence be used as reagents for the diagnosis of cancer, and the like.

The immunological determination of the MDC protein can be made according to any conventional technique. For example, any of the fluorescent antibody technique, the passive agglutination technique and

the enzyme antibody technique may be employed.

(5) Gene analysis of human tumor tissues

5 The biological specimens which can be used for gene analysis include human normal tissues and various types of human tumor tissues, as well as human blood, human body fluids, human secretions and the like. The extraction and preparation of DNA can be carried out, for example, according to the method of Sato et al. (Sato, T. et al., Cancer Res., 50, 7184, 1990).

10 The presence or absence of mutations of the gene can be analyzed by using, as probes, a restriction fragment of the DNA encoding human MDC protein as provided by the present invention, or by selecting a properly located base sequence from the DNA, synthesizing an oligonucleotide having the selected base sequence and using the oligonucleotide as primer.

These analyses can also detect other alterations, such as insertion and deletion, of the gene in samples.

15 The base sequences selected for this purpose can be exon portions, intron portions, or junction portions therebetween. It is a matter of course that artificially modified base sequences may be used. When an artificially modified base sequence is used to prepare primer, the corresponding gene mutation can be detected by the gene analysis.

Analyses can be carried out, for example, by amplifying a partial sequence by PCR using two selected 20 sequences as primers and analyzing the base sequence of the amplification product directly, or by incorporating the amplification product into a plasmid in the same manner as that described above, transforming host cells with this plasmid, culturing the transformed cells, and analyzing the base sequence of the clone thus obtained. Alternatively, the presence or absence of particular mutations of the gene in samples can be directly detected by the use of the ligase chain reaction method (Wu et al., Genomics, 4, 560-569, 1989) and, moreover, the mutant sequence specific PCR method (Ruano and Kidd, Nucleic Acid Research, 17, 8392, 1989; C.R. Newton et al., Nucleic Acid Research, 17, 2503-2517, 1989).

Similarly, using probes containing DNA sequences selected or RNA sequences derived therefrom, point mutations can be detected by the SSCP method or the RNase protection method. Moreover, use of these probes also makes it possible to detect mutations of the gene in samples by Southern hybridization and abnormalities in the expression level of the gene in samples by northern hybridization. 30

Escherichia coli DH5/pBR1 and Escherichia coli XL1-Blue MRF'Kan/pCR-5P2, each carrying a plasmid containing the DNA encoding this MDC protein, and Escherichia coli 490A/cCl 17-904, carrying a cosmid containing the genomic DNA, were deposited with the National Institute of Bioscience and Human-Technology, Agency of Industrial Science and Technology, Ministry of International Trade and Industry on 35 April 28, 1993, February 8, 1994 and April 28, 1993 under accession numbers FERM BP-4286, FERM BP-4555 and FERM BP-4287, respectively.

The MDC proteins and DNAs encoding the MDC proteins according to the present invention are expected to be useful as reagents for cancer research, testing and diagnostic reagents, and therapeutic agents.

40 Examples

The present invention will now be described in more detail with reference to the following Examples which should not be considered to limit the scope of the present invention.

45 Example 1 Isolation of cosmid clones specific for human chromosome 17 and construction of a chromosome map

A human-mouse hybrid cell line (GM10331) containing a single human chromosome 17 in a mouse 50 genomic background was selected from among hybrid cells produced by fusing human normal cells with cells of an established mouse cell line and cosmid clones specific for human chromosome 17 were isolated according to the method of Tokino et al. (Tokino et al., Am. J. Hum. Genet., 48, 258-268, 1991). The chromosomal DNA of this hybrid cell line was properly digested with restriction enzyme Sau 3AI and the ends of the fragments thus obtained were treated by partial filling-in with dATP and dGTP. Fragments 55 having a size of 35-42 kb were separated therefrom and inserted in cosmid vector pWEX15 which had previously been digested with restriction enzyme Xho I and similarly treated at its ends by partial filling-in with dCTP and dTTP. From among the resulting cosmid clones, clones containing human DNA fragments were selected by colony hybridization using ³²P-labeled human chromosomal DNA as probe. Thus, 342

cosmid clones specific for human chromosome 17 were isolated.

With regard to each of these cosmid clones specific for human chromosome 17, the location to which its cosmid DNA hybridize on the chromosome was determined by FISH (Inazawa et al., Genomics, 10, 1075-1078, 1991). Thus, a physical chromosome map for chromosome 17 was constructed (see Tables 1-3 and Fig. 1).

Using DNAs obtained from 6 unrelated individuals, the cosmid clones (cosmid markers), the locations on the chromosome to which their cosmid DNA hybridize had been determined, were examined by a known method (Nakamura et al., Am. J. Hum. Genet., 43, 854-859, 1988) in order to see whether RFLP could be detected or not. The restriction enzyme used was Msp I, Taq I, Bgl II, Pst I, Pvu II, Rsa I or Eco RI. As a result, RFLP was detected in 43 clones (see Tables 4-6). That is, these 43 clones were usable as RFLP markers.

Example 2 Detection of commonly deleted regions of the human chromosome 17q in ovarian and breast cancers

Tumor tissues were obtained from 94 patients with ovarian cancer and 246 patients with breast cancer who underwent surgery. Corresponding normal tissues or peripheral blood samples were also obtained from the respective patients. DNAs were extracted from these tissues or samples according to a known method (Sato et al., Cancer Res., 50, 7184-7189, 1990). Each DNA was digested with suitable restriction enzymes, and the fragments thus obtained were subjected to 1.0% agarose gel electrophoresis and then Southern transferred to a nylon membrane with 0.1N NaOH/0.1M NaCl (Sato et al., Cancer Res., 50, 7184-7189, 1990).

The membranes thus obtained were examined for LOH (loss of heterozygosity) by Southern hybridization (Sato et al., Cancer Res., 50, 7184-7189, 1990) using, as probes, the RFLP markers obtained by the procedure of Example 1 (see Table 7).

Table 7

Probe	Chromosomal location	Enzyme	Ovarian Cancer					Breast Cancer										
			No. of patients tested				allelic losses/informative cases(%)				No. of patients tested				allelic losses/informative cases (%)			
			serous	mucinous	clear cell	others	serous	mucinous	clear cell	others	serous	mucinous	clear cell	others	serous	mucinous	clear cell	others
CI17-316	q12-21.1	MspI	32	15	12	22	6/13(46.2)	0/1(0.0)	0/3(0.0)	1/9(11.1)	85	11/37(29.7)						
CI17-592	q21.3	EcoRI	14	13	9	15	2/3(66.7)	0/1(0.0)	0/1(0.0)	2/4(50.0)	62	8/18(44.4)						
CI17-701	q21.3	TaqI	24	14	13	19	9/15(60.0)	2/12(16.7)	0/7(0.0)	5/12(41.7)	232	48/138(34.8)						
CI17-730	q21.3	TaqI	29	15	13	19	6/12(50.0)	0/4(0.0)	0/4(0.0)	2/4(50.0)	237	36/96(37.5)						
CI17-507	q21.3	MspI	22	14	11	20	6/7(85.7)	1/3(33.3)	1/3(33.3)	2/5(40.0)	74	7/25(28.0)						
CI17-533	q21.3	TaqI	22	13	11	16	6/11(54.5)	3/9(33.3)	1/7(14.3)	4/9(44.4)	230	25/93(26.9)						
CI17-7	q22	PvuII	21	8	9	15	4/5(80.0)	0/1(0.0)	0/3(0.0)	1/3(33.3)	86	14/41(34.1)						
CI17-489	q23	MspI	26	13	11	21	5/5(100.0)	0/2(0.0)	0/3(0.0)	3/8(37.5)	75	10/31(32.3)						
CMH86	q23	TaqI	28	13	10	17	6/17(35.3)	1/8(12.5)	0/6(0.0)	2/10(20.0)	79	12/49(24.5)						
CI17-516	q25.1	TaqI	29	14	14	21	6/17(35.3)	1/10(10.0)	0/7(0.0)	6/11(54.5)	84	9/31(29.0)						
CI17-710	q25.3	TaqI	18	13	10	12	4/8(50.0)	3/8(37.5)	0/6(0.0)	3/7(42.9)	80	13/45(28.9)						

A total of 84 among 94 ovarian tumors were informative for at least one locus, and 33 (39.3%) of them showed LOH for at least one locus on chromosome 17q. Among 246 breast tumors examined, 214 were informative for at least one locus, and 88 (41.4%) showed LOH for at least one locus on chromosome 17q.

From the above results, the instances which were informative for two or more loci and exhibited both loss of heterozygosity at a locus and retaining of heterozygosity at other locus on chromosome 17q were

summarized.

As a result, two commonly deleted regions were found in 8 ovarian cancers (see Fig. 2). One of them was a region lying between markers CI17-316 (17q12-21.1) and CI17-507 (17q21.3), and the other was a region distal to the marker CI17-516 (17q25.1).

Similarly, two commonly deleted regions were found in 35 breast cancers (see Fig. 3). One of them was a region lying between markers CI17-701 (17q21.3) and CI17-730 (17q21.3), which was also found in the ovarian cancers but was more narrowly localized. The other was a region lying on the terminal side of marker CI17-516 (17q25.1), which was also the region where a deletion was observed in the ovarian cancers.

Of the two commonly deleted regions defined by the above-described deletion mapping, the region flanked by markers CI17-701 and CI17-730 was found to lie close to the 17q21 region showing an intimate correlation with the onset of cancer on the basis of the results of linkage mapping studies on hereditary breast cancer and ovarian cancer (Hall et al., *Am. J. Hum. Genet.*, 50, 1235-1242, 1992). The length of this region (i.e., the genetic distance between the two markers) was estimated to be 2.4 cM by linkage analysis (Lathrop et al., *Am. J. Hum. Genet.*, 37, 482-498, 1985; Donis-Keller et al., *Cell*, 51, 319-337, 1987).

Example 3 Isolation of cosmid clones contained in the minimal localized region

Since it has been shown that the region localized on the basis of the results of linkage mapping is a region lying between markers THRA1 and Mfd188 on 17q21 (Hall et al., *Am. J. Hum. Genet.*, 52, 1235-1242, 1992; Bowcock, A.M. et al., *Am. J. Hum. Genet.*, 52, 718-22, 1993), an attempt was made to determine the relative order of these markers and markers CI17-701 and CI17-730 and thereby combine the mapping information obtained by two different strategies. The relative order of the markers was determined by a two-color FISH method newly developed by the present inventors. This method is a modification of FISH in which a highly extended chromosome preparation obtained by synchronization of the cells is used to enhance the degree of fineness and, moreover, probes labeled with fluorescent materials having different colors are used. This method makes it possible to determine the relative order of markers very close to each other.

As a result, it was found that marker Mfd188 lies between markers CI17-701 and CI17-730 and marker THRA1 lies on the centromeric side of CI17-701 (see Fig. 4, a). That is, the region associated with hereditary breast cancer as localized by linkage mapping and the commonly deleted region in sporadic breast cancers as localized by deletion mapping overlapped each other and the overlapping minimal region was flanked by markers CI17-701 and Mfd188 (see Fig. 4, a). When a physical map of this region was constructed by pulsed-field gel electrophoresis, the length of the overlapping region was greatly narrowed down to about 500 kb.

Furthermore, of the cosmid clones obtained by the procedure of Example 1, 37 clones localized to 17q21.3 and three known markers, THRA1, Mfd188 and PPY, were selected and used for fine mapping of this chromosomal region by two-color FISH. As a result, 15 cosmid clones were located in a region flanked by markers CI17-701 and CI17-730. Of these, two cosmid clones, CI17-527 and CI17-904, were found to lie in the above-described overlapping region (see Fig. 4, a and b).

Example 4 Detection of genomic alterations in breast cancers

Of the overlapping region of about 500 kb, about 150 kb has already been covered by four cosmid clones CI17-701, CI17-527, CI17-904 and Mfd188. Accordingly, an attempt was first made to screen restriction (Sac I, Pvu II or Pst I) fragments of the DNAs from the tumor tissues of 650 sporadic breast cancers by Southern-blot analysis using the DNAs of these cosmid clones or fragments thereof as probes and thereby detect gross structural genomic alterations (so-called genomic rearrangements), such as deletion, duplication, amplification and translocation, having occurred in the tumor cells. As a result, when the DNA of CI17-904 or its 9.5 kb Hind III fragment (see Fig. 4, c) was used as probe, genomic rearrangements were detected in the tumor tissues of two breast cancers (see Fig. 5, a and b). These genomic rearrangements occurred only in the tumor tissues, exhibiting extra bands of different size which were not observed in normal tissues. In addition, the intensities of some bands were increased. That is, a gene amplification occurred in a definite DNA region corresponding to (i.e., hybridizable) this probe. In one case among the above-mentioned two breast cancers, no gene amplification was detected when Southern-blot analysis of the Sac I fragments of DNA from the breast cancer tissue was carried out by using the E-H5.2 or Hind6.1 fragment adjacent to the 9.5 kb Hind III fragment (see Fig. 4, c) as probe (see Fig. 6, Case 1). This indicates that the gene amplification in this case occurred within the region corresponding to the 9.5

kb Hind III fragment and was a 4- to 5-fold amplification.

For purpose of closer examination, Southern-blot analyses of the Sac I fragments of DNA from the breast cancer tissue were carried out using each of six Sac I fragments derived from the 9.5 kb Hind III fragment, A, B, C, D, E and F (see Fig. 4, c), as probe. As a result, amplified bands of abnormal size were
 5 observed at 2.5 kb with probes A and B, at 3.0 kb with probes B, C and D, at 2.5 kb with probes E and F, and at 0.9 kb with probe F (see Fig. 7).

In the other case, gene amplification was detected when Southern-blot analysis of the Sac I fragments of DNA from the breast cancer tissue was carried out by using the E-H5.2 fragment as probe (see Fig. 6, Case 2). However, no gene amplification was detected when the Hind6.1 fragment was used as probe (see
 10 Fig. 6, Case 2). In this case, when the E-H5.2 fragment was used as probe, only an amplification was observed without being attended with any band of abnormal size. This indicates that the gene amplification in this case occurred in a segment extending from within the region corresponding to the 9.5 kb HindIII fragment to the outer (telomeric) side of the region corresponding to the E-H5.2 fragment.

15 Example 5 Isolation of cDNA and determination of its structure

In order to isolate an expressed gene in or near the region where genomic rearrangements were detected in the two breast cancers, DNA fragments containing DNA sequences involved in fundamental cellular functions and conserved among other species were selected from DNA fragments of cosmid clone
 20 C117-904. Specifically, each of the DNA fragments of cosmid clone C117-904 was used as probe in Southern blot hybridization analyses of DNA fragments from cow, pig, mouse, rat and chicken. As a result, the 3.5 kb Hind III-Ksp I fragment (see Fig. 4, c) of cosmid clone C117-904 hybridized to DNAs from cow, pig, mouse and rat and showed strong conservation.

Using this 3.5 kb Hind III-Ksp I fragment as probe, human cDNA libraries derived from five different
 25 organs (i.e., mammary gland, breast cancer cell line, fetal brain, cerebrum and cerebellum) were screened. Thus, the longest cDNA was cloned from the cerebellar cDNA library. This cDNA hybridized to the 3.5 kb Hind III-Ksp I fragment of cosmid clone C117-904 and a plurality of adjoining restriction fragments, and extended over a region of more than 20 kb on the chromosome.

Analysis of the base sequence of this cDNA revealed that it consisted of 2923 base pairs (bp) and was
 30 a novel DNA base sequence containing a 5'-untranslated region of 27 bp, a coding region of 1575 bp, a 3'-untranslated region of 1306 bp, and a poly(A) tail of 15 bp (see SEQ ID NO:6). The open reading frame contained in this cDNA sequence encoded a novel protein (MDC protein; see SEQ ID NO:2). An in-frame termination codon was present immediately upstream of the first ATG of the open reading frame. A polyadenylation signal, AATAAA, was observed about 20 bp upstream from the polyadenylation site.

35 Example 6 Determination of the structure of genomic DNA

In order to clarify the structure of the genomic DNA corresponding to the cDNA obtained in Example 5, cosmid clone C117-904 was examined to determine the base sequences of portions containing the base
 40 sequence of this cDNA and portions surrounding them. Then, the sequences of both were compared to determine the exon-intron junctions. As a result, the sequence structure of a novel DNA containing 25 exons corresponding to the cDNA obtained in Example 5 was clarified (see SEQ ID NO:9). Thus, it was shown that these 25 exons are of relatively small size and present over an about 20 kb region of the chromosome.

45 Example 7 Detection of alterations in the exon structure of the gene in breast cancers

From the structure of the DNA containing exons/introns as clarified in Example 6, it has become apparent that exons 2, 3 and 4 are present in the sequence region of the probe (the 9.5 kb Hind III fragment of cosmid clone C117-904) with which alterations were detected in the tumor tissues of two breast cancers
 50 as described in Example 4. More specifically, exon 2 is present in the sequence region of probe E, and exons 3 and 4 are present in the sequence region of probe F (see Fig. 4, c). Accordingly, it is believed that the gene rearrangements involving the 9.5 kb Hind III fragment region as described in Example 4 disrupt the normal exon structure in the region containing the three exons of the gene. In order to confirm this, the chromosomal DNAs from the tumor tissues of the above-described two breast cancers were examined by
 55 Southern-blot analysis using probes having DNA sequences corresponding to exons 2, 3 and 4. Thus, amplified bands of abnormal size were observed similarly to the previously described results obtained with probe E or F (see Fig. 7).

Example 8 Tissue specificity of gene expression

mRNAs derived from various human tissues (brain, heart, kidney, liver, lung, pancreas, placenta, skeletal muscle, colon, peripheral blood lymphocyte, ovary, small intestine, spleen, testis and thymus) were examined by northern-blot analysis using the cDNA obtained in Example 5 as probe. As a result, the strongest expression was observed in the brain, and a weak expression in the heart, ovary and testis.

Moreover, amplification by RT-PCR (reverse-transcriptase PCR) was performed to detect a weaker expression. Specifically, using random hexamers as primers, single-stranded cDNAs were synthesized from mRNAs derived from various human tissues under the action of reverse transcriptase. Then, PCR amplification from these templates was performed using primers BCO9 and BCO12 having sequences derived from the sequences of exons 21 and 23, respectively, which had been revealed in Example 6. As a result, a PCR product having the expected size was observed mainly in tissues of the central nervous system (cerebrum, cerebellum and fetal brain) and in endocrine or reproductive organs (testis, ovary, mammary gland, adrenal gland, thymus and pancreas).

The sequences of the primers used are as follows:

BCO9 5'-GCACCTGCCCCGGCAGT-3' (SEQ ID NO:10) (coding strand, corresponding to base numbers 1764-1780 of SEQ ID NO:6)
BCO12 5'-CCAGGACAGCCCCAGCGATG-3' (SEQ ID NO:11) (antisense strand, corresponding to base numbers 1976-1957 of SEQ ID NO:6)

Example 9 Direct sequencing of mRNA by RT-PCR

mRNAs derived from human fetal brain and human testis were amplified by RT-PCR using primer GMA701 having a sequence derived from the sequence on exon 19 and primer GMB704 having a sequence derived from the sequence on exon 21. Then, the base sequences of the amplified DNAs were directly determined using primer GMA702 or GMB703. As a result, a sequence, wherein 10 bases (base numbers 1512-1521) were deleted from the cerebellar cDNA sequence of SEQ ID NO:6 obtained in Example 5, was found, which revealed the expression of mRNA corresponding to the DNA sequence of SEQ ID NO:7. Both of the fetal brain and testis mRNAs gave the identical result. The open reading frame contained in the cDNA sequence of SEQ ID NO:7 encodes an MDC protein (see SEQ ID NO:3) composed of 670 amino acids.

This seems to be caused by the alternative RNA splicing at the initiation of exon 20 which starts with base number 6083 instead of base number 6078 on the genomic DNA of SEQ ID NO:9. Such a variation of splicing is also known from, for example, a report by Oda et al. [Biochem. Biophys. Res. Commun., 193, 897-904 (1993)]. As a result, the amino acid sequences encoded by the cDNA of SEQ ID NO:6 and the cDNA of SEQ ID NO:7 differ from each other at and after that site (see SEQ ID NO:2 and SEQ ID NO:3). Specifically, the cDNA of SEQ ID NO:6 produces a termination codon within exon 20, whereas the reading frame is shifted in the cDNA of SEQ ID NO:7 so as to cause the open reading frame to continue to a more downstream position.

The sequences of the primers used in PCR and DNA sequencing are as follows:

GMA701 5'-GGCTGCTGATCGCTTCTGCTAC-3' (SEQ ID NO:12) (coding strand, corresponding to base numbers 1413-1434 in SEQ ID NO:6)
GMA702 5'-GAGAAGCTGAATGTGGAGGG-3' (SEQ ID NO:13) (coding strand, corresponding to base numbers 1435-1456 in SEQ ID NO:6)
GMB703 5'-GTCAGAGCCGTCCGCCAGC-3' (SEQ ID NO:14) (antisense strand, corresponding to base numbers 1675-1657 in SEQ ID NO:6)
GMB704 5'-GCCATCCTCCACATAGCTCAGG-3' (SEQ ID NO:15) (antisense strand, corresponding to base numbers 1696-1655 in SEQ ID NO:6)

Example 10 Amplification of the 5'-terminal sequence by RACE

In order to obtain the full-length cDNA represented by SEQ ID NO:7, PCR amplification of the 5'-cDNA terminus (5'-RACE; Frohman, et al., Proc. Natl. Acad. Sci. USA, 85, 8998-9002, 1988; Belyavski, et al., Nucleic Acid Res., 17, 2919-2932, 1988) was performed. Using specific oligomer SGN012 as primer, together with a commercially available synthesis kit, a single-stranded cDNA was synthesized from 2 µg of poly A(+) RNA derived from human brain (manufactured by Clontech). Then, 5'-RACE was performed using a commercially available kit based on the method of Edwards et al. for linking an anchor oligomer to an end of a single-stranded cDNA (Nucleic Acid Res., 19, 5227-5232, 1991). As a result of PCR using the

anchor oligomer of the kit and another specific oligomer SGN011 as primers, an amplification product of about 580 bp was detected by electrophoresis.

This amplification product was extracted from the electrophoretic gel, purified, inserted in the Srf I cleavage site of plasmid vector pCR-Script (manufactured by Stratagene), and cloned. Plasmid DNA was purified from each clone and its base sequence was determined. One of the clones, pCR-5P2, had a cDNA insert of 501 bp beginning with ATG, next to the sequence of the anchor oligomer. The base sequence of the insert extending from base number 315 onward coincided exactly with the base sequence of SEQ ID NO:7 extending from base number 45 (the initiation site of exon 2) onward, excepting one base which will be mentioned below. Furthermore, as far as the reading frame is concerned, that of pCR-5P2 beginning with the first ATG corresponded with the polypeptide encoded by the cDNA of SEQ ID NO:7. The N-terminal region of the polypeptide sequence thus obtained encoded a signal peptide comprising a series of hydrophobic amino acids.

RT-PCR was performed in order to confirm that the above 5'-terminal sequence obtained by 5'-RACE was truly linked, on mRNA, to the sequence of SEQ ID NO:7 extending from base number 45 onward. Using random hexamers as primers, single-stranded cDNAs were synthesized from poly A(+) RNAs derived from human brain, fetal brain, ovary and testis (manufactured by Clontech). Then, the cDNA template were amplified by PCR using an oligomer (SGN013) having the first 20-base sequence of pCR-5P2 as sense primer and SGN011 or SGN012 as antisense primer. As a result, the expected amplification product (about 500 bp for SGN013/SGN011 and about 750 bp for SGN013/SGN012) was detected by electrophoresis with every tissue RNA used.

Thus, it was confirmed that the 5'-terminal sequence of pCR-5P2 obtained by 5'-RACE was linked, on mRNA, to the sequence of SEQ ID NO:7 extending from base number 45 onward, resulting in the construction of a cDNA represented by SEQ ID NO:8. The open reading frame of the cDNA of SEQ ID NO:8 encodes an MDC protein composed of 769 amino acids (see SEQ ID NO:4).

The sequences of the specific oligomers used are as follows:

25	SGN011	5'-GATGTAAGTCAAGTTCCCATCAGAGA-3' (SEQ ID NO:16) (antisense strand, corresponding to base numbers 231-206 in SEQ ID NO:7)
	SGN012	5'-AACAGCTGGTGGTCGTTGATCACAA-3' (SEQ ID NO:17) (antisense strand, corresponding to base numbers 485-461 in SEQ ID NO:7)
30	SGN013	5'-ATGAGGCTGCTGCGGCGCTG-3' (SEQ ID NO:18) (coding strand, corresponding to base numbers 1-20 in SEQ ID NO:8)

The above-mentioned one base in the SEQ ID NO:8 after the initiation site of exon 2, differing from one in the SEQ ID NO:6 or SEQ ID NO:7, is the forth base from the initiation site of exon 2, i.e., the C at the base number 318 in the SEQ ID NO:8. The corresponding base in the SEQ ID NO:6 or the SEQ ID NO:7 is the A at the base number 48. The base C at the base number 318 in the SEQ ID NO:8 codes His at the amino acid number 106 in the SEQ ID NO:4. The base A at the base number 48 in the SEQ ID NO:6 or the SEQ ID NO:7 codes Gln at the amino acid number 7 in the SEQ ID NO:2 or the SEQ ID NO:3. This fact reflects polymorphism.

An amino acid sequence common to these three variant MDC proteins (SEQ ID NO:2, SEQ ID NO:3 and SEQ ID NO:4) is a sequence composed of 488 amino acids (see SEQ ID NO:1), and a DNA sequence encoding this portion is also a common sequence (see SEQ ID NO:5).

Example 11 Homology with known proteins

The amino acid sequences of MDC proteins showed homology with a family of snake venom hemorrhagic proteins including HR1B (Takeya et al., J. Biol. Chem., 265, 16068-16073, 1990), pro-rhodostomin (Au et al., Biochem. Biophys. Res. Commun., 181, 585-593, 1991) and protrigramin (Neeper et al., Nucleic Acid Res., 18, 4255, 1990).

They also showed homology with the guinea pig sperm surface protein PH30 (Blobel et al., Nature, 356, 248-252, 1992) and the rat or monkey epididymis protein EAPI (Perry et al., Biochem. J., 286, 671-675, 1992).

The homology of these proteins with the MDC proteins represented by SEQ ID NO:2 (524 amino acids) and SEQ ID NO:4 (769 amino acids) is indicated by the following "percent identity/number of amino acids in the tested region". The values for SEQ ID NO:2 are given on the left side and those for SEQ ID NO:4 on the right side.

HR1B	32.5/335	32.2/379
prorhodostomin	29.0/420	29.0/420
protrigramin	27.7/430	28.1/438
PH30b	38.1/147	30.8/302
EAP1 (rat)	36.0/364	33.1/475
EAP1 (monkey)	30.4/503	29.9/599

10 Example 12 Generation of transformants

A DNA fragment encoding a part of the MDC protein represented by SEQ ID NO:2 was amplified from the DNA (SEQ ID NO:6) encoding the MDC protein (SEQ ID NO:2) by PCR using primers SGN006 and SGN008. The sequences of the primers used are as follows.

- 15 SGN006 5'-CACAGATCTGGGGGCATATGCTCCCTG-3' (SEQ ID NO:19) (coding strand, corresponding to base numbers 766-783 in SEQ ID NO:6)
- SGN008 5'-AACAAAGCTTCTACTGATGTCTCCACC-3' (SEQ ID NO:20) (antisense strand, corresponding to base numbers 1602-1585 in SEQ ID NO:6; the underline designating a termination codon.)

20 For purposes of vector construction, the 5'-terminal of these primers are provided with Bgl II and Hind III cleavage site sequences, respectively.

The PCR amplification product was separated by agarose gel electrophoresis and cleaved with Bgl II and Hind III. The resulting DNA fragments encoding a part of the MDC protein was combined with vector pMAL-c2 (manufactured by New England Biolabs) which had previously been cleaved with Bam HI and Hind III to construct plasmid pMAL-MDC(C1).

Similarly, the same DNA fragment was combined with vector pQE-13 (manufactured by Diagen) which had previously been cleaved with Bam HI and Hind III to construct plasmid pH6-MDC(C1).

Furthermore, a DNA sequence downstream from the Bam HI cleavage site (base number 1483 in SEQ ID NO:6) was removed from the MDC protein encoding region of pMAL-MDC(C1) by cleaving pMAL-MDC(C1) with Bam HI and Hind III, and recombining it after the formation of blunt ends. This resulted in the construction of plasmid pMAL-MDC(dC1), which mediates expression of a polypeptide with amino acid sequence common to two variant MDC proteins (SEQ ID NO:2 and SEQ ID NO:3).

Since the fragment incorporated into vector pMAL-c2 is expressed as a fusion protein having a maltose-binding protein (MBP) on the N-terminal side, this fusion protein was purified by affinity chromatography using an amylose column. On the other hand, since the fragment incorporated into vector pQE-13 is expressed as a fusion protein having a peptide (His 6) composed of six histidine residues on the N-terminal side, this fusion protein was purified by affinity chromatography using a metal chelate column.

Several transformants were obtained by transforming *E. coli* JM109 with each of plasmids pMAL-MDC(C1), pMAL-MDC(dC1) and pH6-MDC(C1) and selecting for ampicillin resistance.

40 Example 13 Expression and purification of recombinant MDC proteins

Each of the transformants obtained in Example 12 was grown and the resulting recombinant MDC fusion protein was extracted and purified from the culture.

45 Specifically, 100 ml of LB medium (1% polypeptone, 0.5% yeast extract, 1% NaCl) was inoculated with each transformant and incubated overnight at 37°C with shaking. The culture was diluted 10-fold with LB medium previously warmed to 37°C and incubated for additional 30-90 minutes to obtain a culture in the logarithmic growth phase. To 1 liter of the culture was added IPTG (isopropyl-β-D-thiogalactopyranoside) so as to give a final concentration of 1 mM. This culture was incubated for 3-4 hours and then centrifuged to collect the cells therefrom.

50 In the case of transformant of plasmid pMAL-MDC(C1) or pMAL-MDC(dC1), the cells were suspended in 10 ml of a column buffer (20 mM Tris-HCl, pH 7.4, 200 mM NaCl) and disintegrated by sonication. Since the recombinant MDC fusion protein was present in the insoluble fraction of the disintegrated cell suspension, this was separated by centrifugation and dissolved in a denaturing buffer (8M urea, 20 mM Tris-HCl, pH 8.5, 10 mM dithiothreitol). Then, this solution was dialyzed against the column buffer and centrifuged to collect a supernatant soluble fraction. The dialyzed insoluble fraction was further denatured, dialyzed and centrifuged repeatedly to collect additional supernatant soluble fractions. The combined soluble fraction was applied to an amylose column (manufactured by New England Biolabs), which was

washed with the column buffer and eluted with the column buffer containing 10 mM maltose. The eluted fractions were analyzed by absorptiometry at 280 nm and SDS-polyacrylamide electrophoresis (with Coomassie Blue staining), and combined into fractions. As a result, a fraction in which the desired MBP (maltose binding protein) fusion protein (about 68 Kd) was detected as a principal band was obtained for each of the transformants generated with plasmids pMAL-MDC(C1) and pMAL-MDC(dC1). The yield was 46.4 mg and 10.0 mg (when an OD₂₈₀ of 1 was taken as 1 mg/ml), respectively. These fusion proteins will hereinafter be referred to as MBP-MDC(C1) and MBP-MDC(dC1), respectively.

Similarly, in the case of transformant of plasmid pH6-MDC(C1), the cells were suspended in 10 ml of a sonication buffer (10 mM sodium phosphate, pH 8.0, 200 mM NaCl) and disintegrated by sonication. Since the recombinant MDC fusion protein was present in the insoluble fraction of the disintegrated cell suspension, this was separated by centrifugation and dissolved in buffer A (6M guanidine hydrochloride, 100 mM NaH₂PO₄, 10 mM Tris-HCl, pH 8.0). Then, this solution was centrifuged to collect a supernatant soluble fraction, which was applied to a Ni-NTA column (manufactured by Diagen). This column was washed with buffer A and then buffer B (8M urea, 100 mM NaH₂PO₄, 10 mM Tris-HCl, pH 8.0), and eluted stepwise with buffer C (8M urea, 100 mM NaH₂PO₄, 10 mM Tris-HCl, pH 6.3), buffer D (8M urea, 100 mM NaH₂PO₄, 10 mM Tris-HCl, pH 5.9), buffer E (8M urea, 100 mM NaH₂PO₄, 10 mM Tris-HCl, pH 4.5) and buffer F (6M guanidine hydrochloride, 200 mM acetic acid). The eluted fractions were analyzed by absorptiometry at 280 nm and SDS-polyacrylamide electrophoresis (with Coomassie Blue staining), and combined into fractions. As a result, a fraction in which the desired His6 fusion protein (about 34 Kd) was detected as a single band was obtained from the effluent resulting from elution with buffer F. The yield was 51.9 mg (when an OD₂₈₀ of 1 was taken as 1 mg/ml). This fusion protein will hereinafter be referred to as His6-MDC(C1).

Example 14 Preparation of a monoclonal antibody and a rabbit polyclonal antibody

The three recombinant fusion proteins, His6-MDC(C1), MBP-MDC(dC1) and MBP-MDC(C1), obtained in Example 13 were used as an immunizing antigen, an antigen for antibody purification and screening, and a standard antigen for measurement, respectively.

An anti-MDC protein specific monoclonal antibody was prepared by immunizing a mouse with His6-MDC(C1). Specifically, a solution of His6-MDC(C1) (500-1000 µg/ml) in 3 M urea/PBS was mixed with complete adjuvant at a ratio of 1:1, and this mixture was injected into the peritoneal cavity of a mouse at a dose of 100 µg per animal. This injection was repeated 4-6 times at intervals of 2 weeks. After completion of the immunization, hybridomas were produced by fusing P3U1 cells with B cells in the presence of PEG1500. Then, hybridomas productive of an anti-MDC protein specific antibody were selected by monitoring the antibody titer in the culture supernatant.

In order to measure the antibody titer, a first reaction was effected by adding 100 µl of the culture supernatant to a polystyrene cup having a solid phase formed from the MBP-MDC(dC1) fusion protein obtained in Example 13 (5 µg/ml). After washing, a second reaction was effected by the addition of anti-mouse IgG HRP (horse-raddish peroxidase). After washing, a color reaction (third reaction) was effected by the addition of an enzyme substrate solution [i.e., a mixed solution of hydrogen peroxide and ABTS [2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)]], and the produced color was monitored.

The hybridomas were grown on a 96-well multi-plate and screened by means of HAT medium. After about 2 weeks, clones reacting specifically with the antigen were selected by measuring the antibody titer in the culture supernatant. As a result of further cloning, 3 clones (G1-5A2-2C8, G2-2F2-3D11 and G2-2D10-3F5) were established as antibody-producing hybridomas. The class and subclass of the antibody produced by each of the established clones was IgG₁ for G1-5A2-2C8, IgG_{2b} for G2-2F2-3D11, and IgM for G2-2D10-3F5. 3,000,000 cells of each hybridoma were introduced into the peritoneal cavity of a BALB/c mouse to which 0.5 ml of pristane had been administered intraperitoneally about one week before. After 8-10 days, the ascites was collected. From the ascites collected from each animal, an antibody was purified by affinity chromatography using a protein G column.

Similarly, an anti-MDC protein polyclonal antibody was prepared by immunizing a rabbit with an immunizing antigen comprising His6-MDC(C1) obtained in Example 13.

Specifically, like the mouse, a rabbit was immunized with a mixture prepared by mixing a solution of His6-MDC(C1) (500-1000 µg/ml) in 3 M urea/PBS with complete adjuvant at a ratio of 1:1. After completion of the immunization, an antiserum was obtained and its antibody titer was measured using a polystyrene cup having a solid phase formed from the MBP-MDC(dC1) fusion protein obtained in Example 13. The antiserum was diluted 500- to 64,000-fold, 100 µl each of the dilutions were added to wells, and their antibody titers were tested with goat anti-rabbit IgG-HRP. Thus, the antibody titer was detectable up to the

64,000-fold dilution. Since no antibody reacting with MBP-MDC(dC1) was present in the serum before immunization, it could be confirmed that an antibody reacting specifically with the protein was produced. Furthermore, this antiserum was purified by affinity chromatography using a protein G column and a Sepharose column having the MBP-MDC(dC1) fusion protein immobilized therein.

5 A method for the determination of the MDC protein by ELISA using the purified monoclonal antibody and purified rabbit polyclonal antibody obtained in the above-described manner was established.

Specifically, the purified monoclonal antibody derived from a hybridoma (G2-2F2-3D11) was immobilized on a 96-well plate and blocked with BSA (bovine serum albumin). Test solutions containing purified MBP-MDC(C1) at concentrations of 0.156 to 5.00 $\mu\text{g/ml}$ were prepared, added to wells in an amount of 100 μl per well, and reacted at room temperature for an hour. After the wells were washed, a solution (5 $\mu\text{g/ml}$) of the purified rabbit polyclonal antibody was added in an amount of 100 μl per well and reacted at room temperature for an hour. After the wells were washed, anti-rabbit IgG-HRP (5 $\mu\text{g/ml}$) was added in an amount of 100 μl per well and reacted at room temperature for an hour. After completion of the reaction, 2 mM sodium azide was added in an amount of 100 μl per well and the absorbances at 405 nm and 490 nm were measured. It was confirmed that the differential absorbances thus obtained were closely correlated with the concentrations of the test solutions, exhibiting an approximately linear relationship in the range of 0 to 2.5 $\mu\text{g/ml}$ (see Fig. 8). This indicates that ELISA using these monoclonal antibody and rabbit polyclonal antibody can be used as a method for the determination of the MDC protein.

SEQUENCE LISTING

5

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS

10

(A) LENGTH: 488 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

15

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:

20

(A) ORGANISM: Homo sapiens

(vii) INTERMEDIATE SOURCE:

(A) LIBRARY: human fetal brain cDNA library

25

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

30

Leu Leu Ser Ser Gln Tyr Val Glu Arg His Phe Ser Arg Glu Gly Thr
 1 5 10 15

Thr Gln His Ser Thr Gly Ala Gly Asp His Cys Tyr Tyr Gln Gly Lys
 20 25 30

35

Leu Arg Gly Asn Pro His Ser Phe Ala Ala Leu Ser Thr Cys Gln Gly
 35 40 45

40

Leu His Gly Val Phe Ser Asp Gly Asn Leu Thr Tyr Ile Val Glu Pro
 50 55 60

45

Gln Glu Val Ala Gly Pro Trp Gly Ala Pro Gln Gly Pro Leu Pro His
 65 70 75 80

Leu Ile Tyr Arg Thr Pro Leu Leu Pro Asp Pro Leu Gly Cys Arg Glu
 85 90 95

50

55

Pro Gly Cys Leu Phe Ala Val Pro Ala Gln Ser Ala Pro Pro Asn Arg
100 105 110

5 Pro Arg Leu Arg Arg Lys Arg Gln Val Arg Arg Gly His Pro Thr Val
115 120 125

10 His Ser Glu Thr Lys Tyr Val Glu Leu Ile Val Ile Asn Asp His Gln
130 135 140

15 Leu Phe Glu Gln Met Arg Gln Ser Val Val Leu Thr Ser Asn Phe Ala
145 150 155 160

Lys Ser Val Val Asn Leu Ala Asp Val Ile Tyr Lys Glu Gln Leu Asn
165 170 175

20 Thr Arg Ile Val Leu Val Ala Met Glu Thr Trp Ala Asp Gly Asp Lys
180 185 190

25 Ile Gln Val Gln Asp Asp Leu Leu Glu Thr Leu Ala Arg Leu Met Val
195 200 205

Tyr Arg Arg Glu Gly Leu Pro Glu Pro Ser Asn Ala Thr His Leu Phe
210 215 220

30 Ser Gly Arg Thr Phe Gln Ser Thr Ser Ser Gly Ala Ala Tyr Val Gly
225 230 235 240

35 Gly Ile Cys Ser Leu Ser His Gly Gly Gly Val Asn Glu Tyr Gly Asn
245 250 255

40 Met Gly Ala Met Ala Val Thr Leu Ala Gln Thr Leu Gly Gln Asn Leu
260 265 270

Gly Met Met Trp Asn Lys His Arg Ser Ser Ala Gly Asp Cys Lys Cys
275 280 285

45 Pro Asp Ile Trp Leu Gly Cys Ile Met Glu Asp Thr Gly Phe Tyr Leu
290 295 300

50 Pro Arg Lys Phe Ser Arg Cys Ser Ile Asp Glu Tyr Asn Gln Phe Leu
305 310 315 320

55

5 Gln Glu Gly Gly Gly Ser Cys Leu Phe Asn Lys Pro Leu Lys Leu Leu
 325 330 335
 Asp Pro Pro Glu Cys Gly Asn Gly Phe Val Glu Ala Gly Glu Glu Cys
 340 345 350
 10 Asp Cys Gly Ser Val Gln Glu Cys Ser Arg Ala Gly Gly Asn Cys Cys
 355 360 365
 Lys Lys Cys Thr Leu Thr His Asp Ala Met Cys Ser Asp Gly Leu Cys
 15 370 375 380
 Cys Arg Arg Cys Lys Tyr Glu Pro Arg Gly Val Ser Cys Arg Glu Ala
 385 390 395 400
 20 Val Asn Glu Cys Asp Ile Ala Glu Thr Cys Thr Gly Asp Ser Ser Gln
 405 410 415
 Cys Pro Pro Asn Leu His Lys Leu Asp Gly Tyr Tyr Cys Asp His Glu
 25 420 425 430
 Gln Gly Arg Cys Tyr Gly Gly Arg Cys Lys Thr Arg Asp Arg Gln Cys
 30 435 440 445
 Gln Val Leu Trp Gly His Ala Ala Ala Asp Arg Phe Cys Tyr Glu Lys
 450 455 460
 35 Leu Asn Val Glu Gly Thr Glu Arg Gly Ser Cys Gly Arg Lys Gly Ser
 465 470 475 480
 Gly Trp Val Gln Cys Ser Lys Gln
 40 485 488

(2) INFORMATION FOR SEQ ID NO: 2:

45 (1) SEQUENCE CHARACTERISTICS
 (A) LENGTH: 524 amino acids
 (B) TYPE: amino acid
 50 (D) TOPOLOGY: linear
 55

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(vii) INTERMEDIATE SOURCE:

(A) LIBRARY: human fetal brain cDNA library

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

Met Cys Trp Leu Ser His Gln Leu Leu Ser Ser Gln Tyr Val Glu Arg
1 5 10 15

His Phe Ser Arg Glu Gly Thr Thr Gln His Ser Thr Gly Ala Gly Asp
20 25 30

His Cys Tyr Tyr Gln Gly Lys Leu Arg Gly Asn Pro His Ser Phe Ala
35 40 45

Ala Leu Ser Thr Cys Gln Gly Leu His Gly Val Phe Ser Asp Gly Asn
50 55 60

Leu Thr Tyr Ile Val Glu Pro Gln Glu Val Ala Gly Pro Trp Gly Ala
65 70 75 80

Pro Gln Gly Pro Leu Pro His Leu Ile Tyr Arg Thr Pro Leu Leu Pro
85 90 95

Asp Pro Leu Gly Cys Arg Glu Pro Gly Cys Leu Phe Ala Val Pro Ala
100 105 110

Gln Ser Ala Pro Pro Asn Arg Pro Arg Leu Arg Arg Lys Arg Gln Val
115 120 125

Arg Arg Gly His Pro Thr Val His Ser Glu Thr Lys Tyr Val Glu Leu
130 135 140

Ile Val Ile Asn Asp His Gln Leu Phe Glu Gln Met Arg Gln Ser Val
145 150 155 160

	Val	Leu	Thr	Ser	Asn	Phe	Ala	Lys	Ser	Val	Val	Asn	Leu	Ala	Asp	Val	
					165					170					175		
5	Ile	Tyr	Lys	Glu	Gln	Leu	Asn	Thr	Arg	Ile	Val	Leu	Val	Ala	Met	Glu	
				180					185						190		
10	Thr	Trp	Ala	Asp	Gly	Asp	Lys	Ile	Gln	Val	Gln	Asp	Asp	Leu	Leu	Glu	
			195					200					205				
15	Thr	Leu	Ala	Arg	Leu	Met	Val	Tyr	Arg	Arg	Glu	Gly	Leu	Pro	Glu	Pro	
		210					215					220					
20	Ser	Asn	Ala	Thr	His	Leu	Phe	Ser	Gly	Arg	Thr	Phe	Gln	Ser	Thr	Ser	
	225					230					235					240	
25	Ser	Gly	Ala	Ala	Tyr	Val	Gly	Gly	Ile	Cys	Ser	Leu	Ser	His	Gly	Gly	
					245					250					255		
30	Gly	Val	Asn	Glu	Tyr	Gly	Asn	Met	Gly	Ala	Met	Ala	Val	Thr	Leu	Ala	
				260					265						270		
35	Gln	Thr	Leu	Gly	Gln	Asn	Leu	Gly	Met	Met	Trp	Asn	Lys	His	Arg	Ser	
			275					280					285				
40	Ser	Ala	Gly	Asp	Cys	Lys	Cys	Pro	Asp	Ile	Trp	Leu	Gly	Cys	Ile	Met	
		290					295					300					
45	Glu	Asp	Thr	Gly	Phe	Tyr	Leu	Pro	Arg	Lys	Phe	Ser	Arg	Cys	Ser	Ile	
	305					310					315					320	
50	Asp	Glu	Tyr	Asn	Gln	Phe	Leu	Gln	Glu	Gly	Gly	Gly	Ser	Cys	Leu	Phe	
				325					330						335		
55	Asn	Lys	Pro	Leu	Lys	Leu	Leu	Asp	Pro	Pro	Glu	Cys	Gly	Asn	Gly	Phe	
			340					345					350				
60	Val	Glu	Ala	Gly	Glu	Glu	Cys	Asp	Cys	Gly	Ser	Val	Gln	Glu	Cys	Ser	
			355					360					365				
65	Arg	Ala	Gly	Gly	Asn	Cys	Cys	Lys	Lys	Cys	Thr	Leu	Thr	His	Asp	Ala	
		370					375					380					

Met Cys Ser Asp Gly Leu Cys Cys Arg Arg Cys Lys Tyr Glu Pro Arg
 385 390 395 400

Gly Val Ser Cys Arg Glu Ala Val Asn Glu Cys Asp Ile Ala Glu Thr
 405 410 415

Cys Thr Gly Asp Ser Ser Gln Cys Pro Pro Asn Leu His Lys Leu Asp
 420 425 430

Gly Tyr Tyr Cys Asp His Glu Gln Gly Arg Cys Tyr Gly Gly Arg Cys
 435 440 445

Lys Thr Arg Asp Arg Gln Cys Gln Val Leu Trp Gly His Ala Ala Ala
 450 455 460

Asp Arg Phe Cys Tyr Glu Lys Leu Asn Val Glu Gly Thr Glu Arg Gly
 465 470 475 480

Ser Cys Gly Arg Lys Gly Ser Gly Trp Val Gln Cys Ser Lys Gln Pro
 485 490 495

Gln Gln Gly Arg Ala Val Trp Leu Pro Pro Leu Cys Gln His Leu Trp
 500 505 510

Ser Ser Ser Ala Arg Gly Pro Gly Gly Arg His Gln
 515 520 524

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 670 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(vii) INTERMEDIATE SOURCE:

(A) LIBRARY: human fetal brain cDNA library

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

5 Met Cys Trp Leu Ser His Gln Leu Leu Ser Ser Gln Tyr Val Glu Arg
 1 5 10 15
 10 His Phe Ser Arg Glu Gly Thr Thr Gln His Ser Thr Gly Ala Gly Asp
 20 25 30
 15 His Cys Tyr Tyr Gln Gly Lys Leu Arg Gly Asn Pro His Ser Phe Ala
 35 40 45
 20 Ala Leu Ser Thr Cys Gln Gly Leu His Gly Val Phe Ser Asp Gly Asn
 50 55 60
 25 Leu Thr Tyr Ile Val Glu Pro Gln Glu Val Ala Gly Pro Trp Gly Ala
 65 70 75 80
 30 Pro Gln Gly Pro Leu Pro His Leu Ile Tyr Arg Thr Pro Leu Leu Pro
 85 90 95
 35 Asp Pro Leu Gly Cys Arg Glu Pro Gly Cys Leu Phe Ala Val Pro Ala
 100 105 110
 40 Gln Ser Ala Pro Pro Asn Arg Pro Arg Leu Arg Arg Lys Arg Gln Val
 115 120 125
 45 Arg Arg Gly His Pro Thr Val His Ser Glu Thr Lys Tyr Val Glu Leu
 130 135 140
 50 Ile Val Ile Asn Asp His Gln Leu Phe Glu Gln Met Arg Gln Ser Val
 145 150 155 160
 55 Val Leu Thr Ser Asn Phe Ala Lys Ser Val Val Asn Leu Ala Asp Val
 165 170 175
 60 Ile Tyr Lys Glu Gln Leu Asn Thr Arg Ile Val Leu Val Ala Met Glu
 180 185 190

Thr Trp Ala Asp Gly Asp Lys Ile Gln Val Gln Asp Asp Leu Leu Glu
 195 200 205
 5 Thr Leu Ala Arg Leu Met Val Tyr Arg Arg Glu Gly Leu Pro Glu Pro
 210 215 220
 10 Ser Asn Ala Thr His Leu Phe Ser Gly Arg Thr Phe Gln Ser Thr Ser
 225 230 235 240
 Ser Gly Ala Ala Tyr Val Gly Gly Ile Cys Ser Leu Ser His Gly Gly
 245 250 255
 15 Gly Val Asn Glu Tyr Gly Asn Met Gly Ala Met Ala Val Thr Leu Ala
 260 265 270
 20 Gln Thr Leu Gly Gln Asn Leu Gly Met Met Trp Asn Lys His Arg Ser
 275 280 285
 Ser Ala Gly Asp Cys Lys Cys Pro Asp Ile Trp Leu Gly Cys Ile Met
 25 290 295 300
 Glu Asp Thr Gly Phe Tyr Leu Pro Arg Lys Phe Ser Arg Cys Ser Ile
 30 305 310 315 320
 Asp Glu Tyr Asn Gln Phe Leu Gln Glu Gly Gly Gly Ser Cys Leu Phe
 325 330 335
 35 Asn Lys Pro Leu Lys Leu Leu Asp Pro Pro Glu Cys Gly Asn Gly Phe
 340 345 350
 Val Glu Ala Gly Glu Glu Cys Asp Cys Gly Ser Val Gln Glu Cys Ser
 40 355 360 365
 Arg Ala Gly Gly Asn Cys Cys Lys Lys Cys Thr Leu Thr His Asp Ala
 370 375 380
 45 Met Cys Ser Asp Gly Leu Cys Cys Arg Arg Cys Lys Tyr Glu Pro Arg
 385 390 395 400
 50 Gly Val Ser Cys Arg Glu Ala Val Asn Glu Cys Asp Ile Ala Glu Thr
 405 410 415
 55

Cys Thr Gly Asp Ser Ser Gln Cys Pro Pro Asn Leu His Lys Leu Asp
 420 425 430

5 Gly Tyr Tyr Cys Asp His Glu Gln Gly Arg Cys Tyr Gly Gly Arg Cys
 435 440 445

10 Lys Thr Arg Asp Arg Gln Cys Gln Val Leu Trp Gly His Ala Ala Ala
 450 455 460

Asp Arg Phe Cys Tyr Glu Lys Leu Asn Val Glu Gly Thr Glu Arg Gly
 465 470 475 480

15 Ser Cys Gly Arg Lys Gly Ser Gly Trp Val Gln Cys Ser Lys Gln Asp
 485 490 495

20 Val Leu Cys Gly Phe Leu Leu Cys Val Asn Ile Ser Gly Ala Pro Arg
 500 505 510

25 Leu Gly Asp Leu Val Gly Asp Ile Ser Ser Val Thr Phe Tyr His Gln
 515 520 525

Gly Lys Glu Leu Asp Cys Arg Gly Gly His Val Gln Leu Ala Asp Gly
 530 535 540

30 Ser Asp Leu Ser Tyr Val Glu Asp Gly Thr Ala Cys Gly Pro Asn Met
 545 550 555 560

35 Leu Cys Leu Asp His Arg Cys Leu Pro Ala Ser Ala Phe Asn Phe Ser
 565 570 575

40 Thr Cys Pro Gly Ser Gly Glu Arg Arg Ile Cys Ser His His Gly Val
 580 585 590

Cys Ser Asn Glu Gly Lys Cys Ile Cys Gln Pro Asp Trp Thr Gly Lys
 595 600 605

45 Asp Cys Ser Ile His Asn Pro Leu Pro Thr Ser Pro Pro Thr Gly Glu
 610 615 620

50 Thr Glu Arg Tyr Lys Gly Pro Ser Gly Thr Asn Ile Ile Ile Gly Ser
 625 630 635 640

55

Ile Ala Gly Ala Val Leu Val Ala Ala Ile Val Leu Gly Gly Thr Gly
645 650 655

Trp Gly Phe Lys Asn Ile Arg Arg Gly Arg Ser Gly Gly Ala
660 665 670

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 769 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(vii) INTERMEDIATE SOURCE:

(A) LIBRARY: human fetal brain cDNA library

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

Met Arg Leu Leu Arg Arg Trp Ala Phe Ala Ala Leu Leu Leu Ser Leu
1 5 10 15

Leu Pro Thr Pro Gly Leu Gly Thr Gln Gly Pro Ala Gly Ala Leu Arg
20 25 30

Trp Gly Gly Leu Pro Gln Leu Gly Gly Pro Gly Ala Pro Glu Val Thr
35 40 45

Glu Pro Ser Arg Leu Val Arg Glu Ser Ser Gly Gly Glu Val Arg Lys
50 55 60

Gln Gln Leu Asp Thr Arg Val Arg Gln Glu Pro Pro Gly Gly Pro Pro
65 70 75 80

Val His Leu Ala Gln Val Ser Phe Val Ile Pro Ala Phe Asn Ser Asn
85 90 95

EP 0 633 268 A2

Phe Thr Leu Asp Leu Glu Leu Asn His His Leu Leu Ser Ser Gln Tyr
100 105 110

5 Val Glu Arg His Phe Ser Arg Glu Gly Thr Thr Gln His Ser Thr Gly
115 120 125

10 Ala Gly Asp His Cys Tyr Tyr Gln Gly Lys Leu Arg Gly Asn Pro His
130 135 140

15 Ser Phe Ala Ala Leu Ser Thr Cys Gln Gly Leu His Gly Val Phe Ser
145 150 155 160

Asp Gly Asn Leu Thr Tyr Ile Val Glu Pro Gln Glu Val Ala Gly Pro
165 170 175

20 Trp Gly Ala Pro Gln Gly Pro Leu Pro His Leu Ile Tyr Arg Thr Pro
180 185 190

25 Leu Leu Pro Asp Pro Leu Gly Cys Arg Glu Pro Gly Cys Leu Phe Ala
195 200 205

Val Pro Ala Gln Ser Ala Pro Pro Asn Arg Pro Arg Leu Arg Arg Lys
210 215 220

30 Arg Gln Val Arg Arg Gly His Pro Thr Val His Ser Glu Thr Lys Tyr
225 230 235 240

35 Val Glu Leu Ile Val Ile Asn Asp His Gln Leu Phe Glu Gln Met Arg
245 250 255

Gln Ser Val Val Leu Thr Ser Asn Phe Ala Lys Ser Val Val Asn Leu
260 265 270

40 Ala Asp Val Ile Tyr Lys Glu Gln Leu Asn Thr Arg Ile Val Leu Val
275 280 285

45 Ala Met Glu Thr Trp Ala Asp Gly Asp Lys Ile Gln Val Gln Asp Asp
290 295 300

50 Leu Leu Glu Thr Leu Ala Arg Leu Met Val Tyr Arg Arg Glu Gly Leu
305 310 315 320

55

EP 0 633 268 A2

Pro Glu Pro Ser Asn Ala Thr His Leu Phe Ser Gly Arg Thr Phe Gln
325 330 335

5 Ser Thr Ser Ser Gly Ala Ala Tyr Val Gly Gly Ile Cys Ser Leu Ser
340 345 350

10 His Gly Gly Gly Val Asn Glu Tyr Gly Asn Met Gly Ala Met Ala Val
355 360 365

15 Thr Leu Ala Gln Thr Leu Gly Gln Asn Leu Gly Met Met Trp Asn Lys
370 375 380

His Arg Ser Ser Ala Gly Asp Cys Lys Cys Pro Asp Ile Trp Leu Gly
385 390 395 400

20 Cys Ile Met Glu Asp Thr Gly Phe Tyr Leu Pro Arg Lys Phe Ser Arg
405 410 415

25 Cys Ser Ile Asp Glu Tyr Asn Gln Phe Leu Gln Glu Gly Gly Gly Ser
420 425 430

Cys Leu Phe Asn Lys Pro Leu Lys Leu Leu Asp Pro Pro Glu Cys Gly
435 440 445

30 Asn Gly Phe Val Glu Ala Gly Glu Glu Cys Asp Cys Gly Ser Val Gln
450 455 460

35 GGlu Cys Ser Arg Ala Gly Gly Asn Cys Cys Lys Lys Cys Thr Leu Thr
465 470 475 480

His Asp Ala Met Cys Ser Asp Gly Leu Cys Cys Arg Arg Cys Lys Tyr
485 490 495

40 Glu Pro Arg Gly Val Ser Cys Arg Glu Ala Val Asn Glu Cys Asp Ile
500 505 510

45 Ala Glu Thr Cys Thr Gly Asp Ser Ser Gln Cys Pro Pro Asn Leu His
515 520 525

50 Lys Leu Asp Gly Tyr Tyr Cys Asp His Glu Gln Gly Arg Cys Tyr Gly
530 535 540

55

Gly Arg Cys Lys Thr Arg Asp Arg Gln Cys Gln Val Leu Trp Gly His
 545 550 555 560
 5
 Ala Ala Ala Asp Arg Phe Cys Tyr Glu Lys Leu Asn Val Glu Gly Thr
 565 570 575
 10
 Glu Arg Gly Ser Cys Gly Arg Lys Gly Ser Gly Trp Val Gln Cys Ser
 580 585 590
 15
 Lys Gln Asp Val Leu Cys Gly Phe Leu Leu Cys Val Asn Ile Ser Gly
 595 600 605
 20
 Ala Pro Arg Leu Gly Asp Leu Val Gly Asp Ile Ser Ser Val Thr Phe
 610 615 620
 Tyr His Gln Gly Lys Glu Leu Asp Cys Arg Gly Gly His Val Gln Leu
 625 630 635 640
 25
 Ala Asp Gly Ser Asp Leu Ser Tyr Val Glu Asp Gly Thr Ala Cys Gly
 645 650 655
 30
 Pro Asn Met Leu Cys Leu Asp His Arg Cys Leu Pro Ala Ser Ala Phe
 660 665 670
 Asn Phe Ser Thr Cys Pro Gly Ser Gly Glu Arg Arg Ile Cys Ser His
 675 680 685
 35
 His Gly Val Cys Ser Asn Glu Gly Lys Cys Ile Cys Gln Pro Asp Trp
 690 695 700
 40
 Thr Gly Lys Asp Cys Ser Ile His Asn Pro Leu Pro Thr Ser Pro Pro
 705 710 715 720
 Thr Gly Glu Thr Glu Arg Tyr Lys Gly Pro Ser Gly Thr Asn Ile Ile
 725 730 735
 45
 Ile Gly Ser Ile Ala Gly Ala Val Leu Val Ala Ala Ile Val Leu Gly
 740 745 750
 50
 Gly Thr Gly Trp Gly Phe Lys Asn Ile Arg Arg Gly Arg Ser Gly Gly
 755 760 765
 55

Ala
769

5 (2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS

10 (A) LENGTH: 1464 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: double

15 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA to mRNA

20 (vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(vii) INTERMEDIATE SOURCE:

25 (A) LIBRARY: human fetal brain cDNA library

(ix) FEATURE

30 (A) NAME/KEY: CDS

(B) LOCATION: 1..1464

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

35 CTC CTC TCC TCG CAA TAC GTG GAG CGC CAC TTC AGC CGG GAG GGG ACA 48
 Leu Leu Ser Ser Gln Tyr Val Glu Arg His Phe Ser Arg Glu Gly Thr
 1 5 10 15

40 ACC CAG CAC AGC ACC GGG GCT GGA GAC CAC TGC TAC TAC CAG GGG AAG 96
 Thr Gln His Ser Thr Gly Ala Gly Asp His Cys Tyr Tyr Gln Gly Lys
 20 25 30

45 CTC CGG GGG AAC CCG CAC TCC TTC GCC GCC CTC TCC ACC TGC CAG GGG 144
 Leu Arg Gly Asn Pro His Ser Phe Ala Ala Leu Ser Thr Cys Gln Gly
 35 40 45

5	CTG CAT GGG GTC TTC TCT GAT GGG AAC TTG ACT TAC ATC GTG GAG CCC Leu His Gly Val Phe Ser Asp Gly Asn Leu Thr Tyr Ile Val Glu Pro	192
	50 55 60	
10	CAA GAG GTG GCT GGA CCT TGG GGA GCC CCT CAG GGA CCC CTT CCC CAC Gln Glu Val Ala Gly Pro Trp Gly Ala Pro Gln Gly Pro Leu Pro His	240
	65 70 75 80	
15	CTC ATT TAC CGG ACC CCT CTC CTC CCA GAT CCC CTC GGA TGC AGG GAA Leu Ile Tyr Arg Thr Pro Leu Leu Pro Asp Pro Leu Gly Cys Arg Glu	288
	85 90 95	
20	CCA GGC TGC CTG TTT GCT GTG CCT GCC CAG TCG GCT CCT CCA AAC CGG Pro Gly Cys Leu Phe Ala Val Pro Ala Gln Ser Ala Pro Pro Asn Arg	336
	100 105 110	
25	CCG AGG CTG AGA AGG AAA AGG CAG GTC CGC CGG GGC CAC CCT ACA GTG Pro Arg Leu Arg Arg Lys Arg Gln Val Arg Arg Gly His Pro Thr Val	384
	115 120 125	
30	CAC AGT GAA ACC AAG TAT GTG GAG CTA ATT GTG ATC AAC GAC CAC CAG His Ser Glu Thr Lys Tyr Val Glu Leu Ile Val Ile Asn Asp His Gln	432
	130 135 140	
35	CTG TTC GAG CAG ATG CGA CAG TCG GTG GTC CTC ACC AGC AAC TTT GCC Leu Phe Glu Gln Met Arg Gln Ser Val Val Leu Thr Ser Asn Phe Ala	480
	145 150 155 160	
40	AAG TCC GTG GTG AAC CTG GCC GAT GTG ATA TAC AAG GAG CAG CTC AAC Lys Ser Val Val Asn Leu Ala Asp Val Ile Tyr Lys Glu Gln Leu Asn	528
	165 170 175	
45	ACT CGC ATC GTC CTG GTT GCC ATG GAA ACA TGG GCA GAT GGG GAC AAG Thr Arg Ile Val Leu Val Ala Met Glu Thr Trp Ala Asp Gly Asp Lys	576
	180 185 190	
50	ATC CAG GTG CAG GAT GAC CTC CTG GAG ACC CTG GCC CGG CTC ATG GTC Ile Gln Val Gln Asp Asp Leu Leu Glu Thr Leu Ala Arg Leu Met Val	624
	195 200 205	
55		

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TAC	CGA	CGG	GAG	GGT	CTG	CCT	GAG	CCC	AGT	AAT	GCC	ACC	CAC	CTC	TTC	672
Tyr	Arg	Arg	Glu	Gly	Leu	Pro	Glu	Pro	Ser	Asn	Ala	Thr	His	Leu	Phe	
	210					215					220					
TCG	GGC	AGG	ACC	TTC	CAG	AGC	ACG	AGC	AGC	GGG	GCA	GCC	TAC	GTG	GGG	720
Ser	Gly	Arg	Thr	Phe	Gln	Ser	Thr	Ser	Ser	Gly	Ala	Ala	Tyr	Val	Gly	
	225				230					235					240	
GGC	ATA	TGC	TCC	CTG	TCC	CAT	GGC	GGG	GGT	GTG	AAC	GAG	TAC	GGC	AAC	768
Gly	Ile	Cys	Ser	Leu	Ser	His	Gly	Gly	Gly	Val	Asn	Glu	Tyr	Gly	Asn	
				245					250					255		
ATG	GGG	GCG	ATG	GCC	GTG	ACC	CTT	GCC	CAG	ACG	CTG	GGA	CAG	AAC	CTG	816
Met	Gly	Ala	Met	Ala	Val	Thr	Leu	Ala	Gln	Thr	Leu	Gly	Gln	Asn	Leu	
			260					265					270			
GGC	ATG	ATG	TGG	AAC	AAA	CAC	CGG	AGC	TCG	GCA	GGG	GAC	TGC	AAG	TGT	864
Gly	Met	Met	Trp	Asn	Lys	His	Arg	Ser	Ser	Ala	Gly	Asp	Cys	Lys	Cys	
		275					280					285				
CCA	GAC	ATC	TGG	CTG	GGC	TGC	ATC	ATG	GAG	GAC	ACT	GGG	TTC	TAC	CTG	912
Pro	Asp	Ile	Trp	Leu	Gly	Cys	Ile	Met	Glu	Asp	Thr	Gly	Phe	Tyr	Leu	
	290					295					300					
CCC	CGC	AAG	TTC	TCT	CGC	TGC	AGC	ATC	GAC	GAG	TAC	AAC	CAG	TTT	CTG	960
Pro	Arg	Lys	Phe	Ser	Arg	Cys	Ser	Ile	Asp	Glu	Tyr	Asn	Gln	Phe	Leu	
	305				310					315					320	
CAG	GAG	GGT	GGT	GGC	AGC	TGC	CTC	TTC	AAC	AAG	CCC	CTC	AAG	CTC	CTG	1008
Gln	Glu	Gly	Gly	Gly	Ser	Cys	Leu	Phe	Asn	Lys	Pro	Leu	Lys	Leu	Leu	
				325					330					335		
GAC	CCC	CCA	GAG	TGC	GGG	AAC	GGC	TTC	GTG	GAG	GCA	GGG	GAG	GAG	TGC	1056
Asp	Pro	Pro	Glu	Cys	Gly	Asn	Gly	Phe	Val	Glu	Ala	Gly	Glu	Glu	Cys	
			340					345					350			
GAC	TGC	GGC	TCG	GTG	CAG	GAG	TGC	AGC	CGC	GCA	GGT	GGC	AAC	TGC	TGC	1104
Asp	Cys	Gly	Ser	Val	Gln	Glu	Cys	Ser	Arg	Ala	Gly	Gly	Asn	Cys	Cys	
		355					360					365				

5 AAG AAA TGC ACC CTG ACT CAC GAC GCC ATG TGC AGC GAC GGG CTC TGC 1152
 Lys Lys Cys Thr Leu Thr His Asp Ala Met Cys Ser Asp Gly Leu Cys
 370 375 380

10 TGT CGC CGC TGC AAG TAC GAA CCA CGG GGT GTG TCc TGC CGA GAG GCC 1200
 Cys Arg Arg Cys Lys Tyr Glu Pro Arg Gly Val Ser Cys Arg Glu Ala
 385 390 395 400

15 GTG AAC GAG TGC GAC ATC GCG GAG ACC TGC ACC GGG GAC TCT AGC CAG 1248
 Val Asn Glu Cys Asp Ile Ala Glu Thr Cys Thr Gly Asp Ser Ser Gln
 405 410 415

20 TGC CCG CCT AAC CTG CAC AAG CTG GAC GGT TAC TAC TGT GAC CAT GAG 1296
 Cys Pro Pro Asn Leu His Lys Leu Asp Gly Tyr Tyr Cys Asp His Glu
 420 425 430

25 CAG GGC CGC TGC TAC GGA GGT CGC TGC AAA ACC CGG GAC CGG CAG TGC 1344
 Gln Gly Arg Cys Tyr Gly Gly Arg Cys Lys Thr Arg Asp Arg Gln Cys
 435 440 445

30 CAG GTT CTT TGG GGC CAT GCG GCT GCT GAT CGC TTC TGC TAC GAG AAG 1392
 Gln Val Leu Trp Gly His Ala Ala Ala Asp Arg Phe Cys Tyr Glu Lys
 450 455 460

35 CTG AAT GTG GAG GGG ACG GAG CGT GGG AGC TGT GGG CGC AAG GGA TCC 1440
 Leu Asn Val Glu Gly Thr Glu Arg Gly Ser Cys Gly Arg Lys Gly Ser
 465 470 475 480

40 GGC TGG GTC CAG TGC AGT AAG CAG 1464
 Gly Trp Val Gln Cys Ser Lys Gln
 485

(2) INFORMATION FOR SEQ ID NO: 6:

(1) SEQUENCE CHARACTERISTICS

- 45 (A) LENGTH: 2923 base pairs.
 (B) TYPE: nucleic acid
 50 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

55

(ii) MOLECULE TYPE: cDNA to mRNA

(vi) ORIGINAL SOURCE:

5 (A) ORGANISM: Homo sapiens

(vii) INTERMEDIATE SOURCE:

10 (A) LIBRARY: human fetal brain cDNA library

(ix) FEATURE

(A) NAME/KEY: 5' UTR

15 (B) LOCATION: 1..27

(ix) FEATURE

(A) NAME/KEY: 3' UTR

20 (B) LOCATION: 1600..2923

(ix) FEATURE

25 (A) NAME/KEY: CDS

(B) LOCATION: 28..1599

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

30 GCGTTTACTG GCAAACCGCA TTTGTAA ATG TGC TGG CTG AGC CAC CAA CTC 51
Met Cys Trp Leu Ser His Gln Leu
1 5

35 CTC TCC TCG CAA TAC GTG GAG CGC CAC TTC AGC CGG GAG GGG ACA ACC 99
Leu Ser Ser Gln Tyr Val Glu Arg His Phe Ser Arg Glu Gly Thr Thr
10 15 20

40 CAG CAC AGC ACC GGG GCT GGA GAC CAC TGC TAC TAC CAG GGG AAG CTC 147
Gln His Ser Thr Gly Ala Gly Asp His Cys Tyr Tyr Gln Gly Lys Leu
25 30 35 40

45 CGG GGG AAC CCG CAC TCC TTC GCC GCC CTC TCC ACC TGC CAG GGG CTG 195
Arg Gly Asn Pro His Ser Phe Ala Ala Leu Ser Thr Cys Gln Gly Leu
45 50 55

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55

	CAT GGG GTC TTC TCT GAT GGG AAC TTG ACT TAC ATC GTG GAG CCC CAA	243
	His Gly Val Phe Ser Asp Gly Asn Leu Thr Tyr Ile Val Glu Pro Gln	
	60 65 70	
5	GAG GTG GCT GGA CCT TGG GGA GCC CCT CAG GGA CCC CTT CCC CAC CTC	291
	Glu Val Ala Gly Pro Trp Gly Ala Pro Gln Gly Pro Leu Pro His Leu	
	75 80 85	
10	ATT TAC CGG ACC CCT CTC CTC CCA GAT CCC CTC GGA TGC AGG GAA CCA	339
	Ile Tyr Arg Thr Pro Leu Leu Pro Asp Pro Leu Gly Cys Arg Glu Pro	
	90 95 100	
15	GGC TGC CTG TTT GCT GTG CCT GCC CAG TCG GCT CCT CCA AAC CGG CCG	387
	Gly Cys Leu Phe Ala Val Pro Ala Gln Ser Ala Pro Pro Asn Arg Pro	
	105 110 115 120	
20	AGG CTG AGA AGG AAA AGG CAG GTC CGC CGG GGC CAC CCT ACA GTG CAC	435
	Arg Leu Arg Arg Lys Arg Gln Val Arg Arg Gly His Pro Thr Val His	
	125 130 135	
25	AGT GAA ACC AAG TAT GTG GAG CTA ATT GTG ATC AAC GAC CAC CAG CTG	483
	Ser Glu Thr Lys Tyr Val Glu Leu Ile Val Ile Asn Asp His Gln Leu	
	140 145 150	
30	TTC GAG CAG ATG CGA CAG TCG GTG GTC CTC ACC AGC AAC TTT GCC AAG	531
	Phe Glu Gln Met Arg Gln Ser Val Val Leu Thr Ser Asn Phe Ala Lys	
	155 160 165	
35	TCC GTG GTG AAC CTG GCC GAT GTG ATA TAC AAG GAG CAG CTC AAC ACT	579
	Ser Val Val Asn Leu Ala Asp Val Ile Tyr Lys Glu Gln Leu Asn Thr	
	170 175 180	
40	CGC ATC GTC CTG GTT GCC ATG GAA ACA TGG GCA GAT GGG GAC AAG ATC	627
	Arg Ile Val Leu Val Ala Met Glu Thr Trp Ala Asp Gly Asp Lys Ile	
	185 190 195 200	
45	CAG GTG CAG GAT GAC CTC CTG GAG ACC CTG GCC CGG CTC ATG GTC TAC	675
	Gln Val Gln Asp Asp Leu Leu Glu Thr Leu Ala Arg Leu Met Val Tyr	
	205 210 215	

50

55

	CGA CGG GAG GGT CTG CCT GAG CCC AGT AAT GCC ACC CAC CTC TTC TCG	723
	Arg Arg Glu Gly Leu Pro Glu Pro Ser Asn Ala Thr His Leu Phe Ser	
	220 225 230	
5	GGC AGG ACC TTC CAG AGC ACG AGC AGC GGG GCA GCC TAC GTG GGG GGC	771
	Gly Arg Thr Phe Gln Ser Thr Ser Ser Gly Ala Ala Tyr Val Gly Gly	
	235 240 245	
10	ATA TGC TCC CTG TCC CAT GGC GGG GGT GTG AAC GAG TAC GGC AAC ATG	819
	Ile Cys Ser Leu Ser His Gly Gly Gly Val Asn Glu Tyr Gly Asn Met	
	250 255 260	
15	GGG GCG ATG GCC GTG ACC CTT GCC CAG ACG CTG GGA CAG AAC CTG GGC	867
	Gly Ala Met Ala Val Thr Leu Ala Gln Thr Leu Gly Gln Asn Leu Gly	
	265 270 275 280	
20	ATG ATG TGG AAC AAA CAC CGG AGC TCG GCA GGG GAC TGC AAG TGT CCA	915
	Met Met Trp Asn Lys His Arg Ser Ser Ala Gly Asp Cys Lys Cys Pro	
	285 290 295	
25	GAC ATC TGG CTG GGC TGC ATC ATG GAG GAC ACT GGG TTC TAC CTG CCC	963
	Asp Ile Trp Leu Gly Cys Ile Met Glu Asp Thr Gly Phe Tyr Leu Pro	
	300 305 310	
30	CGC AAG TTC TCT CGC TGC AGC ATC GAC GAG TAC AAC CAG TTT CTG CAG	1011
	Arg Lys Phe Ser Arg Cys Ser Ile Asp Glu Tyr Asn Gln Phe Leu Gln	
	315 320 325	
35	GAG GGT GGT GGC AGC TGC CTC TTC AAC AAG CCC CTC AAG CTC CTG GAC	1059
	Glu Gly Gly Gly Ser Cys Leu Phe Asn Lys Pro Leu Lys Leu Leu Asp	
	330 335 340	
40	CCC CCA GAG TGC GGG AAC GGC TTC GTG GAG GCA GGG GAG GAG TGC GAC	1107
	Pro Pro Glu Cys Gly Asn Gly Phe Val Glu Ala Gly Glu Glu Cys Asp	
	345 350 355 360	
45	TGC GGC TCG GTG CAG GAG TGC AGC CGC GCA GGT GGC AAC TGC TGC AAG	1155
	Cys Gly Ser Val Gln Glu Cys Ser Arg Ala Gly Gly Asn Cys Cys Lys	
	365 370 375	

AAA TGC ACC CTG ACT CAC GAC GCC ATG TGC AGC GAC GGG CTC TGC TGT 1203
 Lys Cys Thr Leu Thr His Asp Ala Met Cys Ser Asp Gly Leu Cys Cys
 380 385 390
 5
 CGC CGC TGC AAG TAC GAA CCA CGG GGT GTG TCc TGC CGA GAG GCC GTG 1251
 Arg Arg Cys Lys Tyr Glu Pro Arg Gly Val Ser Cys Arg Glu Ala Val
 395 400 405
 10
 AAC GAG TGC GAC ATC GCG GAG ACC TGC ACC GGG GAC TCT AGC CAG TGC 1299
 Asn Glu Cys Asp Ile Ala Glu Thr Cys Thr Gly Asp Ser Ser Gln Cys
 410 415 420
 15
 CCG CCT AAC CTG CAC AAG CTG GAC GGT TAC TAC TGT GAC CAT GAG CAG 1347
 Pro Pro Asn Leu His Lys Leu Asp Gly Tyr Tyr Cys Asp His Glu Gln
 425 430 435 440
 20
 GGC CGC TGC TAC GGA GGT CGC TGC AAA ACC CGG GAC CGG CAG TGC CAG 1395
 Gly Arg Cys Tyr Gly Gly Arg Cys Lys Thr Arg Asp Arg Gln Cys Gln
 445 450 455
 25
 GTT CTT TGG GGC CAT GCG GCT GCT GAT CGC TTC TGC TAC GAG AAG CTG 1443
 Val Leu Trp Gly His Ala Ala Ala Asp Arg Phe Cys Tyr Glu Lys Leu
 460 465 470
 30
 AAT GTG GAG GGG ACG GAG CGT GGG AGC TGT GGG CGC AAG GGA TCC GGC 1491
 Asn Val Glu Gly Thr Glu Arg Gly Ser Cys Gly Arg Lys Gly Ser Gly
 475 480 485
 35
 TGG GTC CAG TGC AGT AAG CAG CCC CAA CAG GGA CGT GCT GTG TGG CTT 1539
 Trp Val Gln Cys Ser Lys Gln Pro Gln Gln Gly Arg Ala Val Trp Leu
 490 495 500
 40
 CCT CCT CTG TGT CAA CAT CTC TGG AGC TCC TCG GCT AGG GGA CCT GGT 1587
 Pro Pro Leu Cys Gln His Leu Trp Ser Ser Ala Arg Gly Pro Gly
 505 510 515 520
 45
 GGG AGA CAT CAG TAGTGTACC TTCTACCACC AGGGCAAGGA GCTGGACTGC 1639
 Gly Arg His Gln
 524
 50
 AGGGGAGGCC ACGTGCAGCT GGCGGACGGC TCTGACCTGA GCTATGTGGA GGATGGCACA 1699
 55

GCCTGCGGGC CTAACATGTT GTGCCTGGAC CATCGCTGCC TGCCAGCTTC TGCCTTCAAC 1759
 TTCAGCACCT GCCCCGGCAG TGGGGAGCGC CGGATTGCT CCCACCACGG GGTCTGCAGC 1819
 5 AATGAAGGGA AGTGCATCTG TCAGCCAGAC TGGACAGGCA AAGACTGCAG TATCCATAAC 1879
 CCCCTGCCCC CGTCCCCACC CACGGGGGAG ACGGAGAGAT ATAAAGGTCC CAGCGGCACC 1939
 AACATCATCA TTGGCTCCAT CGCTGGGGCT GTCCTGGTTG CAGCCATCGT CCTGGGCGGC 1999
 ACGGGCTGGG GATTTAAAAA CATTGCCCGA GGAAGGTCCG GAGGGGCCTA AGTGCCACCC 2059
 10 TCCTCCCTCC AAGCCTGGCA CCCACCGTCT CGGCCCTGAA CCACGAGGCT GCCCCCATCC 2119
 AGCCACGGAG GGAGGCACCA TGCAAATGTC TTCCAGGTCC AAACCCTTCA ACTCCTGGCT 2179
 CCGCAGGGGT TTGGGTGGGG GCTGTGGCCC TGCCCTTGGC ACCACCAGGG TGGACCAGGC 2239
 CTGGAGGGCA CTTCTCCAC AGTCCCCAC CCACCTCTG CGGCTCAGCC TTGCACACCC 2299
 ACTGCCCCGT GTGAATGTAG CTTCCACCTC ATGGATTGCC ACAGCTCAAC TCGGGGGCAC 2359
 15 CTGGAGGGAT GCCCCAGGC AGCCACCAGT GGACCTAGCC TGGATGGCCC CTCCTTGCAA 2419
 CCAGGCAGCT GAGACCAGG TCTTATCTCT CTGGGACCTA GGGGGACGGG GCTGACATCT 2479
 ACATTTTFTA AAAGTGAATC TTAATCGATG AATGTAAACT CGGGGGTGCT GGGGCCAGGG 2539
 CAGATGTGGG GATGTTTTGA CATTTACAGG AGGCCCCGGA GAAACTGAGG TATGGCCATG 2599
 20 CCCTAGACCC TCCCCAAGGA TGACCACACC CGAAGTCTG TCACTGAGCA CAGTCAGGGG 2659
 CTGGGCATCC CAGCTTGCCC CCGCTTAGCC CCGCTGAGCT TGGAGGAAGT ATGAGTGCTG 2719
 ATTCAAACCA AAGCTGCCTG TGCCATGCC AAGGCCTAGG TTATGGGTAC GGCAACCACA 2779
 TGTCCCAGAT CGTCTCCAAT TCGAAAACAA CCGTCTGCT GTCCCTGTCA GGACACATGG 2839
 25 ATTTTGGCAG GCGGGGGGGG GGTTCTAGAA AATATAGGTT CCTATAATAA AATGGCACCT 2899
 TCCCCCTTTA AAAAAAAAAA AAAA 2923

(2) INFORMATION FOR SEQ ID NO: 7:

30

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 2913 base pairs

35

(B) TYPE: nucleic acid

(C) STRANDEDNESS: double

(D) TOPOLOGY: linear

40

(ii) MOLECULE TYPE: cDNA to mRNA

(vi) ORIGINAL SOURCE:

45

(A) ORGANISM: Homo sapiens

(vii) INTERMEDIATE SOURCE:

(A) LIBRARY: human fetal brain cDNA library

50

55

(ix) FEATURE

(A) NAME/KEY: 5' UTR

(B) LOCATION: 1..27

(ix) FEATURE

(A) NAME/KEY: 3' UTR

(B) LOCATION: 2038..2913

(ix) FEATURE

(A) NAME/KEY: CDS

(B) LOCATION: 28..2037

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

CGGTTTACTG GCAAACCGCA TTTGTAA ATG TGC TGG CTG AGC CAC CAA CTC 51
 Met Cys Trp Leu Ser His Gln Leu

1

5

CTC TCC TCG CAA TAC GTG GAG CGC CAC TTC AGC CGG GAG GGG ACA ACC 99
 Leu Ser Ser Gln Tyr Val Glu Arg His Phe Ser Arg Glu Gly Thr Thr
 10 15 20

CAG CAC AGC ACC GGG GCT GGA GAC CAC TGC TAC TAC CAG GGG AAG CTC 147
 Gln His Ser Thr Gly Ala Gly Asp His Cys Tyr Tyr Gln Gly Lys Leu
 25 30 35 40

CGG GGG AAC CCG CAC TCC TTC GCC GCC CTC TCC ACC TGC CAG GGG CTG 195
 Arg Gly Asn Pro His Ser Phe Ala Ala Leu Ser Thr Cys Gln Gly Leu
 45 50 55

CAT GGG GTC TTC TCT GAT GGG AAC TTG ACT TAC ATC GTG GAG CCC CAA 243
 His Gly Val Phe Ser Asp Gly Asn Leu Thr Tyr Ile Val Glu Pro Gln
 60 65 70

GAG GTG GCT GGA CCT TGG GGA GCC CCT CAG GGA CCC CTT CCC CAC CTC 291
 Glu Val Ala Gly Pro Trp Gly Ala Pro Gln Gly Pro Leu Pro His Leu
 75 80 85

5	ATT TAC CGG ACC CCT CTC CTC CCA GAT CCC CTC GGA TGC AGG GAA CCA	339
	Ile Tyr Arg Thr Pro Leu Leu Pro Asp Pro Leu Gly Cys Arg Glu Pro	
	90 95 100	
10	GGC TGC CTG TTT GCT GTG CCT GCC CAG TCG GCT CCT CCA AAC CGG CCG	387
	Gly Cys Leu Phe Ala Val Pro Ala Gln Ser Ala Pro Pro Asn Arg Pro	
	105 110 115 120	
15	AGG CTG AGA AGG AAA AGG CAG GTC CGC CGG GGC CAC CCT ACA GTG CAC	435
	Arg Leu Arg Arg Lys Arg Gln Val Arg Arg Gly His Pro Thr Val His	
	125 130 135	
20	AGT GAA ACC AAG TAT GTG GAG CTA ATT GTG ATC AAC GAC CAC CAG CTG	483
	Ser Glu Thr Lys Tyr Val Glu Leu Ile Val Ile Asn Asp His Gln Leu	
	140 145 150	
25	TTC GAG CAG ATG CGA CAG TCG GTG GTC CTC ACC AGC AAC TTT GCC AAG	531
	Phe Glu Gln Met Arg Gln Ser Val Val Leu Thr Ser Asn Phe Ala Lys	
	155 160 165	
30	TCC GTG GTG AAC CTG GCC GAT GTG ATA TAC AAG GAG CAG CTC AAC ACT	579
	Ser Val Val Asn Leu Ala Asp Val Ile Tyr Lys Glu Gln Leu Asn Thr	
	170 175 180	
35	CGC ATC GTC CTG GTT GCC ATG GAA ACA TGG GCA GAT GGG GAC AAG ATC	627
	Arg Ile Val Leu Val Ala Met Glu Thr Trp Ala Asp Gly Asp Lys Ile	
	185 190 195 200	
40	CAG GTG CAG GAT GAC CTC CTG GAG ACC CTG GCC CGG CTC ATG GTC TAC	675
	Gln Val Gln Asp Asp Leu Leu Glu Thr Leu Ala Arg Leu Met Val Tyr	
	205 210 215	
45	CGA CGG GAG GGT CTG CCT GAG CCC AGT AAT GCC ACC CAC CTC TTC TCG	723
	Arg Arg Glu Gly Leu Pro Glu Pro Ser Asn Ala Thr His Leu Phe Ser	
	220 225 230	
50	GGC AGG ACC TTC CAG AGC ACG AGC AGC GGG GCA GCC TAC GTG GGG GGC	771
	Gly Arg Thr Phe Gln Ser Thr Ser Ser Gly Ala Ala Tyr Val Gly Gly	
	235 240 245	
55		

5	ATA TGC TCC CTG TCC CAT GGC GGG GGT GTG AAC GAG TAC GGC AAC ATG Ile Cys Ser Leu Ser His Gly Gly Gly Val Asn Glu Tyr Gly Asn Met 250 255 260	819
10	GGG GCG ATG GCC GTG ACC CTT GCC CAG ACG CTG GGA CAG AAC CTG GGC Gly Ala Met Ala Val Thr Leu Ala Gln Thr Leu Gly Gln Asn Leu Gly 265 270 275 280	867
15	ATG ATG TGG AAC AAA CAC CGG AGC TCG GCA GGG GAC TGC AAG TGT CCA Met Met Trp Asn Lys His Arg Ser Ser Ala Gly Asp Cys Lys Cys Pro 285 290 295	915
20	GAC ATC TGG CTG GGC TGC ATC ATG GAG GAC ACT GGG TTC TAC CTG CCC Asp Ile Trp Leu Gly Cys Ile Met Glu Asp Thr Gly Phe Tyr Leu Pro 300 305 310	963
25	CGC AAG TTC TCT CGC TGC AGC ATC GAC GAG TAC AAC CAG TTT CTG CAG Arg Lys Phe Ser Arg Cys Ser Ile Asp Glu Tyr Asn Gln Phe Leu Gln 315 320 325	1011
30	GAG GGT GGT GGC AGC TGC CTC TTC AAC AAG CCC CTC AAG CTC CTG GAC Glu Gly Gly Gly Ser Cys Leu Phe Asn Lys Pro Leu Lys Leu Leu Asp 330 335 340	1059
35	CCC CCA GAG TGC GGG AAC GGC TTC GTG GAG GCA GGG GAG GAG TGC GAC Pro Pro Glu Cys Gly Asn Gly Phe Val Glu Ala Gly Glu Glu Cys Asp 345 350 355 360	1107
40	TGC GGC TCG GTG CAG GAG TGC AGC CGC GCA GGT GGC AAC TGC TGC AAG Cys Gly Ser Val Gln Glu Cys Ser Arg Ala Gly Gly Asn Cys Cys Lys 365 370 375	1155
45	AAA TGC ACC CTG ACT CAC GAC GCC ATG TGC AGC GAC GGG CTC TGC TGT Lys Cys Thr Leu Thr His Asp Ala Met Cys Ser Asp Gly Leu Cys Cys 380 385 390	1203
50	CGC CGC TGC AAG TAC GAA CCA CGG GGT GTG TCC TGC CGA GAG GCC GTG Arg Arg Cys Lys Tyr Glu Pro Arg Gly Val Ser Cys Arg Glu Ala Val 395 400 405	1251

EP 0 633 268 A2

AAC GAG TGC GAC ATC GCG GAG ACC TGC ACC GGG GAC TCT AGC CAG TGC 1299
 Asn Glu Cys Asp Ile Ala Glu Thr Cys Thr Gly Asp Ser Ser Gln Cys
 410 415 420
 5
 CCG CCT AAC CTG CAC AAG CTG GAC GGT TAC TAC TGT GAC CAT GAG CAG 1347
 Pro Pro Asn Leu His Lys Leu Asp Gly Tyr Tyr Cys Asp His Glu Gln
 425 430 435 440
 10
 GGC CGC TGC TAC GGA GGT CGC TGC AAA ACC CGG GAC CGG CAG TGC CAG 1395
 Gly Arg Cys Tyr Gly Gly Arg Cys Lys Thr Arg Asp Arg Gln Cys Gln
 445 450 455
 15
 GTT CTT TGG GGC CAT GCG GCT GCT GAT CGC TTC TGC TAC GAG AAG CTG 1443
 Val Leu Trp Gly His Ala Ala Ala Asp Arg Phe Cys Tyr Glu Lys Leu
 460 465 470
 20
 AAT GTG GAG GGG ACG GAG CGT GGG AGC TGT GGG CGC AAG GGA TCC GGC 1491
 Asn Val Glu Gly Thr Glu Arg Gly Ser Cys Gly Arg Lys Gly Ser Gly
 475 480 485
 25
 TGG GTC CAG TGC AGT AAG CAG GAC GTG CTG TGT GGC TTC CTC CTC TGT 1539
 Trp Val Gln Cys Ser Lys Gln Asp Val Leu Cys Gly Phe Leu Leu Cys
 490 495 500
 30
 GTC AAC ATC TCT GGA GCT CCT CGG CTA GGG GAC CTG GTG GGA GAC ATC 1587
 Val Asn Ile Ser Gly Ala Pro Arg Leu Gly Asp Leu Val Gly Asp Ile
 505 510 515 520
 35
 AGT AGT GTC ACC TTC TAC CAC CAG GGC AAG GAG CTG GAC TGC AGG GGA 1635
 Ser Ser Val Thr Phe Tyr His Gln Gly Lys Glu Leu Asp Cys Arg Gly
 525 530 535
 40
 GGC CAC GTG CAG CTG GCG GAC GGC TCT GAC CTG AGC TAT GTG GAG GAT 1683
 Gly His Val Gln Leu Ala Asp Gly Ser Asp Leu Ser Tyr Val Glu Asp
 540 545 550
 45
 GGC ACA GCC TGC GGG CCT AAC ATG TTG TGC CTG GAC CAT CGC TGC CTG 1731
 Gly Thr Ala Cys Gly Pro Asn Met Leu Cys Leu Asp His Arg Cys Leu
 555 560 565
 50
 55

CCA GCT TCT GCC TTC AAC TTC AGC ACC TGC CCC GGC AGT GGG GAG CGC 1779
 Pro Ala Ser Ala Phe Asn Phe Ser Thr Cys Pro Gly Ser Gly Glu Arg
 570 575 580
 5

CGG ATT TGC TCC CAC CAC GGG GTC TGC AGC AAT GAA GGG AAG TGC ATC 1827
 Arg Ile Cys Ser His His Gly Val Cys Ser Asn Glu Gly Lys Cys Ile
 585 590 595 600
 10

TGT CAG CCA GAC TGG ACA GGC AAA GAC TGC AGT ATC CAT AAC CCC CTG 1875
 Cys Gln Pro Asp Trp Thr Gly Lys Asp Cys Ser Ile His Asn Pro Leu
 605 610 615
 15

CCC ACG TCC CCA CCC ACG GGG GAG ACG GAG AGA TAT AAA GGT CCC AGC 1923
 Pro Thr Ser Pro Pro Thr Gly Glu Thr Glu Arg Tyr Lys Gly Pro Ser
 620 625 630
 20

GGC ACC AAC ATC ATC ATT GGC TCC ATC GCT GGG GCT GTC CTG GTT GCA 1971
 Gly Thr Asn Ile Ile Ile Gly Ser Ile Ala Gly Ala Val Leu Val Ala
 635 640 645
 25

GCC TAC GTC CTG GGC GGC ACG GGC TGG GGA TTT AAA AAC ATT CGC CGA 2019
 Ala Ile Val Leu Gly Gly Thr Gly Trp Gly Phe Lys Asn Ile Arg Arg
 650 655 660
 30

GGA AGG TCC GGA GGG GCC TAAGTGCCAC CCTCCTCCCT CCAAGCCTGG 2067
 Gly Arg Ser Gly Gly Ala
 665 670
 35

CACCCACCGT CTCGGCCCTG AACCACGAGG CTGCCCCCAT CCAGCCACGG AGGGAGGCAC 2127
 CATGCAAATG TCTTCCAGGT CCAAACCCTT CAACTCCTGG CTCCGCAGGG GTTTGGGTGG 2187
 GGGCTGTGGC CCTGCCCTTG GCACCACCAG GGTGGACCAG GCCTGGAGGG CACTTCCTCC 2247
 40 ACAGTCCCCC ACCCACCTCC TGCGGCTCAG CCTTGACAC CCAGTGCCCC GTGTGAATGT 2307
 AGCTTCCACC TCATGGATTG CCACAGCTCA ACTCGGGGGC ACCTGGAGGG ATGCCCCCAG 2367
 GCAGCCACCA GTGGACCTAG CCTGGATGGC CCCTCCTTGC AACCAGGCAG CTGAGACCAG 2427
 GGTCTTATCT CTCTGGGACC TAGGGGGACG GGGCTGACAT CTACATTTTT TAAAACTGAA 2487
 45 TCTTAATCGA TGAATGTAAA CTCGGGGGTG CTGGGGCCAG GGCAGATGTG GGGATGTTTT 2547
 GACATTTACA GGAGGCCCCG GAGAACTGA GGTATGGCCA TGCCCTAGAC CCTCCCCAAG 2607
 GATGACCACA CCCGAAGTCC TGTCAGTGAG CACAGTCAGG GGCTGGGCAT CCCAGCTTGC 2667
 CCCCCTTAG CCCCCTGAG CTTGGAGGAA GTATGAGTGC TGATTCAAAC CAAAGCTGCC 2727
 50 TGTGCCATGC CCAAGGCCTA GGTTATGGGT ACGGCAACCA CATGTCCCAG ATCGTCTCCA 2787
 ATTCGAAAAC AACCGTCCTG CTGTCCCTGT CAGGACACAT GGATTTTGGC AGGGCGGGGG 2847

55

GGGGTTCTAG AAAATATAGG TTCCTATAAT AAAATGGCAC CTTCCCCCTT TAAAAAAAAA 2907
AAAAAA 2913

(2) INFORMATION FOR SEQ ID NO: 8:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 3183 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: double

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA to mRNA

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(vii) INTERMEDIATE SOURCE:

(A) LIBRARY: human fetal brain cDNA library

(ix) FEATURE

(A) NAME/KEY: 3' UTR

(B) LOCATION: 2308..3183

(ix) FEATURE

(A) NAME/KEY: CDS

(B) LOCATION: 1..2307

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

ATG AGG CTG CTG CGG CGC TGG GCG TTC GCG GCT CTG CTG CTG TCG CTG 48
Met Arg Leu Leu Arg Arg Trp Ala Phe Ala Ala Leu Leu Leu Ser Leu
1 5 10 15

CTC CCC ACG CCC GGT CTT GGG ACC CAA GGT ccT GCT GGA GCT CTG Cga 96
Leu Pro Thr Pro Gly Leu Gly Thr Gln Gly Pro Ala Gly Ala Leu Arg
20 25 30

5	TGG GGG GGC TTA CCC CAG CTG GGA GGC CCA GGA GCC CCT GAG GTC ACG	144
	Trp Gly Gly Leu Pro Gln Leu Gly Gly Pro Gly Ala Pro Glu Val Thr	
	35 40 45	
10	GAA CCC AGC CGT CTG GTT AGG GAG AGC TCC GGG GGA GAG GTC CGA AAG	192
	Glu Pro Ser Arg Leu Val Arg Glu Ser Ser Gly Gly Glu Val Arg Lys	
	50 55 60	
15	CAG CAG CTG GAC ACA AGG GTC CGC CAG GAG CCA CCA GGG GGC CCG CCT	240
	Gln Gln Leu Asp Thr Arg Val Arg Gln Glu Pro Pro Gly Gly Pro Pro	
	65 70 75 80	
20	GTC CAT CTG GCC CAG GTG AGT TTC GTC ATC CCA GCC TTC AAC TCA AAC	288
	Val His Leu Ala Gln Val Ser Phe Val Ile Pro Ala Phe Asn Ser Asn	
	85 90 95	
25	TTC ACC CTG GAC CTG GAG CTG AAC CAC CAC CTC CTC TCC TCG CAA TAC	336
	Phe Thr Leu Asp Leu Glu Leu Asn His His Leu Leu Ser Ser Gln Tyr	
	100 105 110	
30	GTG GAG CGC CAC TTC AGC CGG GAG GGG ACA ACC CAG CAC AGC ACC GGG	384
	Val Glu Arg His Phe Ser Arg Glu Gly Thr Thr Gln His Ser Thr Gly	
	115 120 125	
35	GCT GGA GAC CAC TGC TAC TAC CAG GGG AAG CTC CGG GGG AAC CCG CAC	432
	Ala Gly Asp His Cys Tyr Tyr Gln Gly Lys Leu Arg Gly Asn Pro His	
	130 135 140	
40	TCC TTC GCC GCC CTC TCC ACC TGC CAG GGG CTG CAT GGG GTC TTC TCT	480
	Ser Phe Ala Ala Leu Ser Thr Cys Gln Gly Leu His Gly Val Phe Ser	
	145 150 155 160	
45	GAT GGG AAC TTG ACT TAC ATC GTG GAG CCC CAA GAG GTG GCT GGA CCT	528
	Asp Gly Asn Leu Thr Tyr Ile Val Glu Pro Gln Glu Val Ala Gly Pro	
	165 170 175	
50	TGG GGA GCC CCT CAG GGA CCC CTT CCC CAC CTC ATT TAC CGG ACC CCT	576
	Trp Gly Ala Pro Gln Gly Pro Leu Pro His Leu Ile Tyr Arg Thr Pro	
	180 185 190	
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CTC CTC CCA GAT CCC CTC GGA TGC AGG GAA CCA GGC TGC CTG TTT GCT	624
Leu Leu Pro Asp Pro Leu Gly Cys Arg Glu Pro Gly Cys Leu Phe Ala	
195 200 205	
GTG CCT GCC CAG TCG GCT CCT CCA AAC CGG CCG AGG CTG AGA AGG AAA	672
Val Pro Ala Gln Ser Ala Pro Pro Asn Arg Pro Arg Leu Arg Arg Lys	
210 215 220	
AGG CAG GTC CGC CGG GGC CAC CCT ACA GTG CAC AGT GAA ACC AAG TAT	720
Arg Gln Val Arg Arg Gly His Pro Thr Val His Ser Glu Thr Lys Tyr	
225 230 235 240	
GTG GAG CTA ATT GTG ATC AAC GAC CAC CAG CTG TTC GAG CAG ATG CGA	768
Val Glu Leu Ile Val Ile Asn Asp His Gln Leu Phe Glu Gln Met Arg	
245 250 255	
CAG TCG GTG GTC CTC ACC AGC AAC TTT GCC AAG TCC GTG GTG AAC CTG	816
Gln Ser Val Val Leu Thr Ser Asn Phe Ala Lys Ser Val Val Asn Leu	
260 265 270	
GCC GAT GTG ATA TAC AAG GAG CAG CTC AAC ACT CGC ATC GTC CTG GTT	864
Ala Asp Val Ile Tyr Lys Glu Gln Leu Asn Thr Arg Ile Val Leu Val	
275 280 285	
GCC ATG GAA ACA TGG GCA GAT GGG GAC AAG ATC CAG GTG CAG GAT GAC	912
Ala Met Glu Thr Trp Ala Asp Gly Asp Lys Ile Gln Val Gln Asp Asp	
290 295 300	
CTC CTG GAG ACC CTG GCC CGG CTC ATG GTC TAC CGA CGG GAG GGT CTG	960
Leu Leu Glu Thr Leu Ala Arg Leu Met Val Tyr Arg Arg Glu Gly Leu	
305 310 315 320	
CCT GAG CCC AGT AAT GCC ACC CAC CTC TTC TCG GGC AGG ACC TTC CAG	1008
Pro Glu Pro Ser Asn Ala Thr His Leu Phe Ser Gly Arg Thr Phe Gln	
325 330 335	
AGC ACG AGC AGC GGG GCA GCC TAC GTG GGG GGC ATA TGC TCC CTG TCC	1056
Ser Thr Ser Ser Gly Ala Ala Tyr Val Gly Gly Ile Cys Ser Leu Ser	
340 345 350	

CAT GGC GGG GGT GTG AAC GAG TAC GGC AAC ATG GGG GCG ATG GCC GTG 1104
 His Gly Gly Gly Val Asn Glu Tyr Gly Asn Met Gly Ala Met Ala Val
 355 360 365

5
 ACC CTT GCC CAG ACG CTG GGA CAG AAC CTG GGC ATG ATG TGG AAC AAA 1152
 Thr Leu Ala Gln Thr Leu Gly Gln Asn Leu Gly Met Met Trp Asn Lys
 370 375 380

10
 CAC CGG AGC TCG GCA GGG GAC TGC AAG TGT CCA GAC ATC TGG CTG GGC 1200
 His Arg Ser Ser Ala Gly Asp Cys Lys Cys Pro Asp Ile Trp Leu Gly
 385 390 395 400

15
 TGC ATC ATG GAG GAC ACT GGG TTC TAC CTG CCC CGC AAG TTC TCT CGC 1248
 Cys Ile Met Glu Asp Thr Gly Phe Tyr Leu Pro Arg Lys Phe Ser Arg
 405 410 415

20
 TGC AGC ATC GAC GAG TAC AAC CAG TTT CTG CAG GAG GGT GGT GGC AGC 1296
 Cys Ser Ile Asp Glu Tyr Asn Gln Phe Leu Gln Glu Gly Gly Gly Ser
 420 425 430

25
 TGC CTC TTC AAC AAG CCC CTC AAG CTC CTG GAC CCC CCA GAG TGC GGG 1344
 Cys Leu Phe Asn Lys Pro Leu Lys Leu Leu Asp Pro Pro Glu Cys Gly
 435 440 445

30
 AAC GGC TTC GTG GAG GCA GGG GAG GAG TGC GAC TGC GGC TCG GTG CAG 1392
 Asn Gly Phe Val Glu Ala Gly Glu Glu Cys Asp Cys Gly Ser Val Gln
 450 455 460

35
 GAG TGC AGC CGC GCA GGT GGC AAC TGC TGC AAG AAA TGC ACC CTG ACT 1440
 Glu Cys Ser Arg Ala Gly Gly Asn Cys Cys Lys Lys Cys Thr Leu Thr
 465 470 475 480

40
 CAC GAC GCC ATG TGC AGC GAC GGG CTC TGC TGT CGC CGC TGC AAG TAC 1488
 His Asp Ala Met Cys Ser Asp Gly Leu Cys Cys Arg Arg Cys Lys Tyr
 485 490 495

45
 GAA CCA CGG GGT GTG TCC TGC CGA GAG GCC GTG AAC GAG TGC GAC ATC 1536
 Glu Pro Arg Gly Val Ser Cys Arg Glu Ala Val Asn Glu Cys Asp Ile
 500 505 510

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5	GCG GAG ACC TGC ACC GGG GAC TCT AGC CAG TGC CCG CCT AAC CTG CAC	1584
	Ala Glu Thr Cys Thr Gly Asp Ser Ser Gln Cys Pro Pro Asn Leu His	
	515 520 525	
10	AAG CTG GAC GGT TAC TAC TGT GAC CAT GAG CAG GGC CGC TGC TAC GGA	1632
	Lys Leu Asp Gly Tyr Tyr Cys Asp His Glu Gln Gly Arg Cys Tyr Gly	
	530 535 540	
15	GGT CGC TGC AAA ACC CGG GAC CGG CAG TGC CAG GTT CTT TGG GGC CAT	1680
	Gly Arg Cys Lys Thr Arg Asp Arg Gln Cys Gln Val Leu Trp Gly His	
	545 550 555 560	
20	GCG GCT GCT GAT CGC TTC TGC TAC GAG AAG CTG AAT GTG GAG GGG ACG	1728
	Ala Ala Ala Asp Arg Phe Cys Tyr Glu Lys Leu Asn Val Glu Gly Thr	
	565 570 575	
25	GAG CGT GGG AGC TGT GGG CGC AAG GGA TCC GGC TGG GTC CAG TGC AGT	1776
	Glu Arg Gly Ser Cys Gly Arg Lys Gly Ser Gly Trp Val Gln Cys Ser	
	580 585 590	
30	AAG CAG GAC GTG CTG TGT GGC TTC CTC CTC TGT GTC AAC ATC TCT GGA	1824
	Lys Gln Asp Val Leu Cys Gly Phe Leu Leu Cys Val Asn Ile Ser Gly	
	595 600 605	
35	GCT CCT CGG CTA GGG GAC CTG GTG GGA GAC ATC AGT AGT GTC ACC TTC	1872
	Ala Pro Arg Leu Gly Asp Leu Val Gly Asp Ile Ser Ser Val Thr Phe	
	610 615 620	
40	TAC CAC CAG GGC AAG GAG CTG GAC TGC AGG GGA GGC CAC GTG CAG CTG	1920
	Tyr His Gln Gly Lys Glu Leu Asp Cys Arg Gly Gly His Val Gln Leu	
	625 630 635 640	
45	GCG GAC GGC TCT GAC CTG AGC TAT GTG GAG GAT GGC ACA GCC TGC GGG	1968
	Ala Asp Gly Ser Asp Leu Ser Tyr Val Glu Asp Gly Thr Ala Cys Gly	
	645 650 655	
50	CCT AAC ATG TTG TGC CTG GAC CAT CGC TGC CTG CCA GCT TCT GCC TTC	2016
	Pro Asn Met Leu Cys Leu Asp His Arg Cys Leu Pro Ala Ser Ala Phe	
	660 665 670	
55		

AAC TTC AGC ACC TGC CCC GGC AGT GGG GAG CGC CGG ATT TGC TCC CAC 2064
 Asn Phe Ser Thr Cys Pro Gly Ser Gly Glu Arg Arg Ile Cys Ser His
 5 675 680 685

CAC GGG GTC TGC AGC AAT GAA GGG AAG TGC ATC TGT CAG CCA GAC TGG 2112
 His Gly Val Cys Ser Asn Glu Gly Lys Cys Ile Cys Gln Pro Asp Trp
 10 690 695 700

ACA GGC AAA GAC TGC AGT ATC CAT AAC CCC CTG CCC ACG TCC CCA CCC 2160
 Thr Gly Lys Asp Cys Ser Ile His Asn Pro Leu Pro Thr Ser Pro Pro
 15 705 710 715 720

ACG GGG GAG ACG GAG AGA TAT AAA GGT CCC AGC GGC ACC AAC ATC ATC 2208
 Thr Gly Glu Thr Glu Arg Tyr Lys Gly Pro Ser Gly Thr Asn Ile Ile
 20 725 730 735

ATT GGC TCC ATC GCT GGG GCT GTC CTG GTT GCA GCC ATC GTC CTG GGC 2256
 Ile Gly Ser Ile Ala Gly Ala Val Leu Val Ala Ala Ile Val Leu Gly
 25 740 745 750

GGC ACG GGC TGG GGA TTT AAA AAC ATT CGC CGA GGA AGG TCC GGA GGC 2304
 Gly Thr Gly Trp Gly Phe Lys Asn Ile Arg Arg Gly Arg Ser Gly Gly
 30 755 760 765

GCC TAAGTGCCAC CCTCCTCCCT CCAAGCCTGG CACCCACCGT CTCGGCCCTG 2357
 Ala
 769

AACCACGAGG CTGCCCCCAT CCAGCCACGG AGGGAGGCAC CATGCAAATG TCTTCCAGGT 2417
 CCAAACCCTT CAACTCCTGG CTCCGCAGGG GTTTGGGTGG GGGCTGTGGC CCTGCCCTTG 2477
 GCACCACCAG GGTGGACCAG GCCTGGAGGG CACTTCCTCC ACAGTCCCCC ACCCACCTCC 2537
 40 TGCGGCTCAG CCTTGCACAC CCACTGCCCC GTGTGAATGT AGCTTCCACC TCATGGATTG 2597
 CCACAGCTCA ACTCGGGGGC ACCTGGAGGG ATGCCCCCAG GCAGCCACCA GTGGACCTAG 2657
 CCTGGATGGC CCCTCCTTGC AACCAGGCAG CTGAGACCAG GGTCTTATCT CTCTGGGACC 2717
 TAGGGGGACG GGGCTGACAT CTACATTTTT TAAAACTGAA TCTTAATCGA TGAATGTAAA 2777
 CTCGGGGGTG CTGGGGCCAG GGCAGATGTG GGGATGTTTT GACATTTACA GGAGGCCCCG 2837
 45 GAGAAACTGA GGTATGGCCA TGCCCTAGAC CCTCCCAAG GATGACCACA CCCGAAGTCC 2897
 TGTCACTGAG CACAGTCAGG GGCTGGGCAT CCCAGCTTGC CCCCCTTAG CCCCCTGAG 2957
 CTTGGAGGAA GTATGAGTGC TGATTCAAAC CAAAGCTGCC TGTGCCATGC CCAAGGCCTA 3017
 GGTATGGGT ACGGCAACCA CATGTCCCAG ATCGTCTCCA ATTCGAAAAC AACCGTCCTG 3077
 50 CTGTCCCTGT CAGGACACAT GGATTTTGGC AGGGCGGGGG GGGTTCTAG AAAATATAGG 3137

55

TTCCTATAAT AAAATGGCAC CTTCCCCCTT TAAAAAAAAA AAAAAA

3183

5 (2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 9278 base pairs

10

(B) TYPE: nucleic acid

(C) STRANDEDNESS: double

15

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(vi) ORIGINAL SOURCE:

20

(A) ORGANISM: Homo sapiens

(vii) INTERMEDIATE SOURCE:

25

(A) LIBRARY: human DNA cosmid library

(ix) FEATURE

(A) NAME/KEY: exon 1

30

(B) LOCATION: 28..44

(ix) FEATURE

35

(A) NAME/KEY: exon 2

(B) LOCATION: 308..374

(ix) FEATURE

40

(A) NAME/KEY: exon 3

(B) LOCATION: 909..994

45

(ix) FEATURE

(A) NAME/KEY: exon 4

50

(B) LOCATION: 1081..1156

55

(ix) FEATURE

5

(A) NAME/KEY: exon 5

(B) LOCATION: 1591..1657

(ix) FEATURE

10

(A) NAME/KEY: exon 6

(B) LOCATION: 1725..1792

(ix) FEATURE

15

(A) NAME/KEY: exon 7

(B) LOCATION: 2182..2256

20

(ix) FEATURE

(A) NAME/KEY: exon 8

25

(B) LOCATION: 2339..2410

(ix) FEATURE

(A) NAME/KEY: exon 9

30

(B) LOCATION: 2588..2754

(ix) FEATURE

35

(A) NAME/KEY: exon 10

(B) LOCATION: 3248..3332

(ix) FEATURE

40

(A) NAME/KEY: exon 11

(B) LOCATION: 3445..3535

45

(ix) FEATURE

(A) NAME/KEY: exon 12

50

(B) LOCATION: 3645..3696

55

(ix) FEATURE

(A) NAME/KEY: exon 13

(B) LOCATION: 4014..4113

(ix) FEATURE

(A) NAME/KEY: exon 14

(B) LOCATION: 4196..4267

(ix) FEATURE

(A) NAME/KEY: exon 15

(B) LOCATION: 4386..4478

(ix) FEATURE

(A) NAME/KEY: exon 16

(B) LOCATION: 4920..5000

(ix) FEATURE

(A) NAME/KEY: exon 17

(B) LOCATION: 5347..5397

(ix) FEATURE

(A) NAME/KEY: exon 18

(B) LOCATION: 5501..5564

(ix) FEATURE

(A) NAME/KEY: exon 19

(B) LOCATION: 5767..5866

(ix) FEATURE

(A) NAME/KEY: exon 20

(B) LOCATION: 6073..6202

(ix) FEATURE

(A) NAME/KEY: exon 21

(B) LOCATION: 6300..6468

(ix) FEATURE

(A) NAME/KEY: exon 22

(B) LOCATION: 6557..6671

(ix) FEATURE

(A) NAME/KEY: exon 23

(B) LOCATION: 6756..6846

(ix) FEATURE

(A) NAME/KEY: exon 24

(B) LOCATION: 7829..7846

(ix) FEATURE

(A) NAME/KEY: exon 25

(B) LOCATION: 8165..9038

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

CGGTTTACTG GCAAACCGCA TTTGTAA ATG TGC TGG CTG AGC CA NNNNNNNNNN 54

Met Cys Trp Leu Ser His
1 5

NNNNCCAGGT GAGTTTCGTC ATCCAGCCTT CAACTCAAAC TTCACCCTGG ACCTGGAGCT 114

GAACCACTGA GNGTGGCCTT GAGCCCAAGA GGAAGGGCAG TGGTGGNNNG GGGGAGACAT 174

GGCTAGGGCC TGGCTGCTGG GGGTCTGGGG GTTGGGCCTG GCGAGAGGGG ACCTGGGTCC 234

TGACCTGAGG CGAGCCTAAA GCCCGACCTC ACCTCGCCCG TGACCCCCCT TCCTGCTGCC 294

CCCTCTGTCT CAG C CAA CTC CTC TCC TCG CAA TAC GTG GAG CGC CAC TTC 344

Gln Leu Leu Ser Ser Gln Tyr Val Glu Arg His Phe
10 15

AGC CGG GAG GGG ACA ACC CAG CAC AGC ACC GTGAGTGCCA CTGCTGGGGA 394
 Ser Arg Glu Gly Thr Thr Gln His Ser Thr

20 25

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CCGGGGCCGG GGATGGAAGG GAGGTGCTGT TTCTGTGGTT CTGTGGTCAC AGGTGTAGGG 454
 ACAGGTGGCC ACTGGAGATG GGGTCCTGGG CCTGGCCCCCT CAGCACCTTC CCTCTCTCCC 514
 GACCCAGGAG GCTCTGAGGG TGGACAGTGG GCAGCTTAGT GCATAGGGCC CTGAAGTCCC 574
 CTCACTTGGC CCCAGAGCTC TGACCCCCAG CCAGCCCACG TGGGGCCTAC AGGGACACTC 634
 GTTCCGAGCA GGCTGCCAGG ATCCNNNNNN NNNNNNATAG ATGACGTGAA GGAGGCCAG 694
 AGGTTCTCTAA CCCAGAGGG CTAGGAACTT GCCCAGGGTG GCACGGCAAA TTAGGAGCAC 754
 CAGCCATCTA GAAACAGGCT CCAGAGCCCC AGGNATACCC AGGGATNGTG GCCACCTGCA 814
 CACAGGGCAG CTTCAAGTGC CCCCCAAAAG CCTTGAGGCC CATTGGCTGC CCCCAGCCTC 874

ATGCCAGCGT TCTGCTCACT GTTCTGCTCC TTAG GGG GCT GGA GAC CAC TGC TAC 929
 Gly Ala Gly Asp His Cys Tyr
 30 35

20

TAC CAG GGG AAG CTC CGG GGG AAC CCG CAC TCC TTC GCC GCC CTC TCC 977
 Tyr Gln Gly Lys Leu Arg Gly Asn Pro His Ser Phe Ala Ala Leu Ser
 40 45 50

25

ACC TGC CAG GGG CTG CA GTGAGTATGG GGAGGGGCCG GGCAGCTGGG 1024
 Thr Cys Gln Gly Leu His
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30

AGAAGCCTCT GGCCCAGGCC TGGGGACGGA GGGGAGCTGC GCCTCTCTCT CCACAG T 1081
 GGG GTC TTC TCT GAT GGG AAC TTG ACT TAC ATC GTG GAG CCC CAA GAG 1129
 Gly Val Phe Ser Asp Gly Asn Leu Thr Tyr Ile Val Glu Pro Gln Glu
 60 65 70

35

GTG GCT GGA CCT TGG GGA GCC CCT CAG GTAAGCCCCA CACAACCCCT 1176
 Val Ala Gly Pro Trp Gly Ala Pro Gln
 75 80

40

TGCCATCCTC TCTGGTGGCC CTGCCAAGCT TGTCCCAACA GCTGTTGCTG CCACCTCTTC 1236
 CTCCTCCGGC TCCTCCCTCA GTAACCCAG CCTCACTGCC CTCTTCAGTG ACCCCAGCTC 1396
 TGGTTCCCTC CCTCCTGTGC CCCAGCTCCC CCTGTGCCCC CAGCTCCAAT GTCCCATCTG 1356
 TCCATAAGT GACCTCCCAT TGGGCTCCAA TGTCCTTTGC CCCTGTCTCT CAGGGTGCCC 1416
 CCAGGTCTTG ACCCCGGAAT CTGAGCATCT GGGAGATCAG ATCCGACATG GGAGCTGTGG 1476
 CCAGTTCTGG GTCACCCAG GGTGGGGTGG AGGCGAGGGC TGGATCTGGC CCCCAGCAAG 1536

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TGGCCTGGAG CAGGCCCACT TGGCACCCCA AGAACTAATT TCCCCTCATT GCAG GGA 1593
 Gly

5 CCC CTT CCC CAC CTC ATT TAC CGG ACC CCT CTC CTC CCA GAT CCC CTC 1641
 Pro Leu Pro His Leu Ile Tyr Arg Thr Pro Leu Leu Pro Asp Pro Leu
 85 90 95

10 GGA TGC AGG GAA CCA G GTAAGGGAGG GGAGGGGGGG TGGGGAGGGG CCNGGCTGTG 1697
 Gly Cys Arg Glu Pro Gly
 100

15 CCCCCCTCAC CTGCCCCCTCC CCGACAG GC TGC CTG TTT GCT GTG CCT GCC CAG 1750
 Cys Leu Phe Ala Val Pro Ala Gln
 105 110

20 TCG GCT CCT CCA AAC CGG CCG AGG CTG AGA AGG AAA AGG CAG 1792
 Ser Ala Pro Pro Asn Arg Pro Arg Leu Arg Arg Lys Arg Gln
 115 120 125

25 GTACGGGGGC CCGCACAGAC CTCGGGCTGC AGAGACCTCG GGCTGCAGAG AGACCTCGGC 1852
 CGTGGCCCAG AGCAGGAGGG CACCCTCATC TATGGCTGGG GCGAAGGAAG GCTCAGATGG 1912
 ATGTGGCTGG GGGCCAGGGA CCGTGTCTGG GAGAAGCCCC CACCCCTTCC CTAATGCTGG 1972
 CATCTACAGA GGCCCCATCC TGGGCAAACC GAGGCTGCCT GCCCTCATTC CAAAGCTGAG 2032
 GAAGGACAGG ACCCTCTGCC AGTGGGGAGC TGGCACTGTC CCTGGCTGGA GTCCAGACCC 2092
 30 CCCCATCCCC ACCGAGTCTG TTCCTGGCTT GGCCATGAGA TCAGTCAGAC ATGGAAGGGA 2152

CTGATTCCAA GTGCCCACCC ACCCCCCAG GTC CGC CGG GGC CAC CCT ACA GTG 2205
 Val Arg Arg Gly His Pro Thr Val
 35 130 135

CAC AGT GAA ACC AAG TAT GTG GAG CTA ATT GTG ATC AAC GAC CAC CAG 2253
 His Ser Glu Thr Lys Tyr Val Glu Leu Ile Val Ile Asn Asp His Gln
 40 140 145 150

CTG GTGAGTGCCA GGGCAGGGAC AGGGCGTGAC ACTGGGAGGC CCCTGAGGAG 2306
 Leu

45 CCTGGCCCTC CTCCCATTCT TCTCTCTCCC AG TTC GAG CAG ATG CGA CAG TCG 2359
 Phe Glu Gln Met Arg Gln Ser
 155

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EP 0 633 268 A2

GTG GTC CTC ACC AGC AAC TTT GCC AAG TCC GTG GTG AAC CTG GCC GAT 2407
Val Val Leu Thr Ser Asn Phe Ala Lys Ser Val Val Asn Leu Ala Asp
160 165 170 175

5

GTG GTAAGCAGCT CTCCCTCCCT CCCTTCCCTC CTCCTCATGC CCCCCACCC 2460
Val

10

CACCACACAC ATTAGGGGGC ACTGTCAGCC CCTGGCTCCC ACTTCCTGGA GAGAACAGAC 2520
AGGCCCTCCT CCAGCCCTGG CCCCACACACC CACTCCACACC CTCCAGCCCC CCTCATCTTC 2580

15

TCCCCAG ATA TAC AAG GAG CAG CTC AAC ACT CGC ATC GTC CTG GTT GCC 2629
Ile Tyr Lys Glu Gln Leu Asn Thr Arg Ile Val Leu Val Ala
180 185 190

20

ATG GAA ACA TGG GCA GAT GGG GAC AAG ATC CAG GTG CAG GAT GAC CTC 2677
Met Glu Thr Trp Ala Asp Gly Asp Lys Ile Gln Val Gln Asp Asp Leu
195 200 205

25

CTG GAG ACC CTG GCC CGG CTC ATG GTC TAC CGA CGG GAG GGT CTG CCT 2725
Leu Glu Thr Leu Ala Arg Leu Met Val Tyr Arg Arg Glu Gly Leu Pro
210 215 220

30

GAG CCC AGT AAT GCC ACC CAC CTC TTC TC GTGAGTCCCC CACCCTGCAC 2774
Glu Pro Ser Asn Ala Thr His Leu Phe Ser
225 230

35

CTCCTGCCAG CCTCTGCTAG TTGCTACAGT GCTTGGGATT ACTTAACACC TGCCCTGTGC 2834
TGGCTGCTCC TCTCAGAGTC TGGGGACTGG GCTCACCTTG CACCTGCCAC CTACCCCCAG 2894
CCACATGCAA CAGCTGGGCA TCATCCCCTG AATCTGAGGT TGATGCCCTT GTCTTAGCCC 2954
TGGTGGTCCT CTTCTGCCTC TCACCTCCCC TTAGTTCTGT CTTTCCCTTC AACTGTCCCN 3014
NNNNNNNNNN NAGAGTGAAA CTCTGTCTCA AAAGAAAAAN AAAANAAAAG AAGAAAAAAA 3074
AGAACCCAAG GAGCGGGGGA AGGGTCTTGC CTGGGGTCAC CAAGGCTGAT GTAAAGGGCC 3134
AGGCTCACCT CCTGAGGAAG GACTCTAGTG TGAGGGGCTC CCAAGGCC CACCACCACC 3194

40

CGGGGAGCCA CAGGGGAGGG CAGAAGCCAT CCTGACAGCG CACTCCCTTC CAG G GGC 3251
Gly

45

AGG ACC TTC CAG AGC ACG AGC AGC GGG GCA GCC TAC GTG GGG GGC ATA 3299
Arg Thr Phe Gln Ser Thr Ser Ser Gly Ala Ala Tyr Val Gly Gly Ile
235 240 245

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5 TGC TCC CTG TCC CAT GGC GGG GGT GTG AAC GAG GTGAGCAGTG 3342
 Cys Ser Leu Ser His Gly Gly Gly Val Asn Glu
 250 255 260

10 GGGGGACATG GCTGGGGTGG CGGCTGAGGG AAAGGGGCTT AGGGGCACGA CGTGCCTGNT 3402
 TGGAAGATGT AGACATCTGT GCCCCATCTT CCCCACCCCC AG TAC GGC AAC ATG 3456
 Tyr Gly Asn Met

15 GGG GCG ATG GCC GTG ACC CTT GCC CAG ACG CTG GGA CAG AAC CTG GGC 3504
 Gly Ala Met Ala Val Thr Leu Ala Gln Thr Leu Gly Gln Asn Leu Gly
 265 270 275 280

20 ATG ATG TGG AAC AAA CAC CGG AGC TCG GCA G GTATCCTCCC CCAGAGGCCC 3555
 Met Met Trp Asn Lys His Arg Ser Ser Ala Gly
 285 290

25 CCGTGTGGCC CAGCAGCTCT GGAACGGGAG GGTGACAGTG GGAGGGGTGG TCCTTGGCCT 3615
 CCCTCATATC CGCCTGGCTC ACCCCTCAG GG GAC TGC AAG TGT CCA GAC ATC 3667
 Asp Cys Lys Cys Pro Asp Ile
 295

30 TGG CTG GGC TGC ATC ATG GAG GAC ACT GG GTGAGTTCTT GGGGACAACC 3716
 Trp Leu Gly Cys Ile Met Glu Asp Thr Gly
 300 305

35 GGGGGAAGGT CTTGGGCGAG GGGAGTCTTA GAGCGAGCAT TGT TTGGCAG TCTGGACCAG 3776
 GGGNNNNNNN NNNNNGAACA CACCTTCCCT TCCAGGCCGG CTTGCGAGTC CCAGGTTCAA 3836
 GCGAGGGATG GGAGCGACAA GGGACAAGGC GGAGGATTCT GGTGCAATCC CGGGGCAGAT 3896
 CCTCCGCCTC CTCGCGATGG TGACGAAGTC CCCCAGTGTA CCCCCTCCCC AGCCTTGAGA 3956
 GGGGTGAGGG TGGGTTGGAG GGGAGCAGCC AGCAGCACCT CCCCTCGCCC TATCCAG G 4014

40 TTC TAC CTG CCC CGC AAG TTC TCT CGC TGC AGC ATC GAC GAG TAC AAC 4062
 Phe Tyr Leu Pro Arg Lys Phe Ser Arg Cys Ser Ile Asp Glu Tyr Asn
 310 315 320

45 CAG TTT CTG CAG GAG GGT GGT GGC AGC TGC CTC TTC AAC AAG CCC CTC 4110
 Gln Phe Leu Gln Glu Gly Gly Gly Ser Cys Leu Phe Asn Lys Pro Leu
 325 330 335 340

50

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AAG GTACCAGCCC CGCGGCGGGG AGCATGGGAG CGGGCCCTGG GCGGGGTCCG 4163
 Lys

5 GGCCAGACTC CCGACCTGTC CTCCCGGTCC AG CTC CTG GAC CCC CCA GAG TGC 4216
 Leu Leu Asp Pro Pro Glu Cys
 345

10 GGG AAC GGC TTC GTG GAG GCA GGG GAG GAG TGC GAC TGC GGC TCG GTG 4264
 Gly Asn Gly Phe Val Glu Ala Gly Glu Glu Cys Asp Cys Gly Ser Val
 350 355 360

15 CAG GTGAGCGGTG GTGCGGGCGC CAGGTGGGGA ACCGGGATGC GGGGGTGGGC 4317
 Gln
 365

20 ACCAGGGAGC GTCTGAGTGG GAGGATTAGG GCTCGCCCGC CTCCTTCCCC TCCTCCCGCG 4377

TCCCTCAG GAG TGC AGC CGC GCA GGT GGC AAC TGC TGC AAG AAA TGC ACC 4427
 Glu Cys Ser Arg Ala Gly Gly Asn Cys Cys Lys Lys Cys Thr
 25 370 375

CTG ACT CAC GAC GCC ATG TGC AGC GAC GGG CTC TGC TGT CGC CGC TGC 4475
 Leu Thr His Asp Ala Met Cys Ser Asp Gly Leu Cys Cys Arg Arg Cys
 30 380 385 390 395

AAG GTAAGCAGGA CCGGCCGGGA GCGGGGGCCA GGACGCAGGA GGAGCGATTG 4528
 Lys

35 GAGGCCTTCA TATAAGGGGT GGGAGCTAGG GAGGGAAGCG GAGCCTTCGG GGACGAAGGC 4588
 CTCTGGGGCA GGGCTTGATG CGAAGACAGC GCCAATGGGA GCAAGGGCGG GCTGAAGGAT 4648
 GTTGAAGGCN NNNNNNNNNN NNNCGGACGG GAAGCTCCCA GAATCAAGGA GGGCGGGAAG 4708
 40 GTGGGCGGGC TTGGGGCGGT GCTGAGTGGC CTGGGAGCGA GGTGGGGAGC GTTCAAGAGG 4768
 TGGTGGGAGC AGGGAATAA GAACAGGCCT AAACGGGGCC CTGGGGAGCT GGAGGGCCCCG 4828
 GGGATGTGGG GGTCCAGAGA GCGGGGGGCC TGGGGAGGGC AGGGCCGAGG CATCCATCCT 4888

45 GCCTGACTCG AGGAGCGCGT CTCTTCCTA G TAC GAA CCA CGG GGT GTG TCC 4940
 Tyr Glu Pro Arg Gly Val Ser
 400

50

55

5 TGC CGA GAG GCC GTG AAC GAG TGC GAC ATC GCG GAG ACC TGC ACC GGG 4988
 Cys Arg Glu Ala Val Asn Glu Cys Asp Ile Ala Glu Thr Cys Thr Gly
 405 410 415

10 GAC TCT AGC CAG GTCCGCCCCG CCCC GCCGTC TTGTGGAGCC CTGGGCGAGG 5040
 Asp Ser Ser Gln
 420

15 CAACCCCTAC CTTGTGCGAT TTGGTTTTCC CGGACGAGTG CTCAGCACTC CCCTCCTCTC 5100
 CACAGCTGGC ATCGACCTTC ACTGATCAGA CTGTTTTCTT ATCTGAGAAA GGGGTTCTTC 5160
 ATGCTCCTGG CTTGTTCTCT TCAATCATT AACCAGAATG TATCGTCTGG CTGGTATCCC 5220
 AGCGCCTGGG CCCGGTGNNN NNNNNNNNTA CCCAGATTCC TCCTGGGCAG CCCTCAGCTC 5280
 CAGTCTGGG CAGCCCTCAG CCCAGTCTG GGA CTGCTCC GCTCAACCCC ACCCTCTCT 5340

20 CCACAG TGC CCG CCT AAC CTG CAC AAG CTG GAC GGT TAC TAC TGT GAC 5388
 Cys Pro Pro Asn Leu His Lys Leu Asp Gly Tyr Tyr Cys Asp
 425 430 435

25 CAT GAG CAG GTATGATGGC TGCCCCCTGA GCCTGGGATT CAGGGCAGTC 5437
 His Glu Gln
 440

30 TCTTATCTCC ACTCTGACCA CTCAGCATCT CCATCCCTTG CCTCTTAATT CTTGGACTCT 5497

35 CAG GGC CGC TGC TAC GGA GGT CGC TGC AAA ACC CGG GAC CGG CAG TGC 5545
 Gly Arg Cys Tyr Gly Gly Arg Cys Lys Thr Arg Asp Arg Gln Cys
 445 450 455

40 CAG GTT CTT TGG GGC CAT G GTGAGTCTGC TAGGGCTGGA GTGGGACTCC 5594
 Gln Val Leu Trp Gly His Ala
 460

45 GGAGGAGCCC AGAGCTGAGA AGCTGGGGAG AGTGGGTTCC AGCTGAACAG GCCCCAAGT 5654
 GTGTAGCTCC CCAGGATCTC AGGGAGCCCA GGCAGAGTGT GGGAGATGCA GGCCTGAGGT 5714

50 CTTGGGGTGG GTCCTGGGGC ACGTGGGGTC ACTTGGCATC CTCTCCCCAC AG CG GCT 5771
 Ala

55 GCT GAT CGC TTC TGC TAC GAG AAG CTG AAT GTG GAG GGG ACG GAG CGT 5819
 Ala Asp Arg Phe Cys Tyr Glu Lys Leu Asn Val Glu Gly Thr Glu Arg
 465 470 475

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GGG AGC TGT GGG CGC AAG GGA TCC GGC TGG GTC CAG TGC AGT AAG CA 5866
 Gly Ser Cys Gly Arg Lys Gly Ser Gly Trp Val Gln Cys Ser Lys Gln
 480 485 490 495

GTGAGTACTG AGGCTCCCAG AGGGCCTCTC AGCTCCAGGG CAGGTGTGAG ACTTTTCAGA 5926
 GATGGGGTAG TAGGTTCTCC CAGGAGGAGC CTGTCAGTCC CAATGGGCGG GCACGTGGCA 5986
 AATGAGGTGG CAGGGTGCAG GGTGAGGGCA GATTAGAGTT CAGTAGTTGA GTCTGAGGTC 6046

AAACCTGGGG CTCACTGTCT CTATAT G CCC CAA CAG GGA CGT GCT GTG TGG 6097
 Pro Gln Gln Gly Arg Ala Val Trp
 500

CTT CCT CCT CTG TGT CAA CAT CTC TGG AGC TCC TCG GCT AGG GGA CCT 6145
 Leu Pro Pro Leu Cys Gln His Leu Trp Ser Ser Ser Ala Arg Gly Pro
 505 510 515

GGT GGG AGA CAT CAG TAGTGTACCC TTCTACCACC AGGGCAAGGA GCTGGACTGC 6200
 Gly Gly Arg His Gln
 520

AGGTGCTGAC CAGCACCAAA ACTCAGGGAG GGGACCTGGC AGCTGTGCTG GGGGTTAGAA 6260
 GATCTGGGGG CTGGAGGCTG GGCTGTGTCA CTTCCCCAGG GGAGGCCACG TGCAGCTGGC 6320
 GGACGGCTCT GACCTGAGCT ATGTGGAGGA TGGCACAGCC TCGGGGCCTA ACATGTTGTG 6380
 CCTGGACCAT CGCTGCCTGC CAGCTTCTGC CTTCAACTTC AGCACCTGCC CCGGCAGTGG 6440
 GGAGCGCCGG ATTTGCTCCC ACCACGGGGT GACTGCCTGG AGCCCGGGAT GGCGGGAGAA 6500
 GCTTACAAGA GGGGACAGGC CCCTGCTCAC CTCTCCTGGC CCTGCCCTGC CTCTAGGTCT 6560
 GCAGCAATGA AGGGAAGTGC ATCTGTACAG CAGACTGGAC AGGCAAAGAC TGCAGTATCC 6620
 ATAACCCCTT GCCCACGTCC CCACCCACGG GGGAGACGGA GAGATATAAA GGTGAGGCTG 6680
 GAGCTGGCCG AGGGGGGTCT GTCTGTCCCG CTCTCTATGC CTGTCCTTGC CAGCTAAGCC 6740
 CTGCCATCCT CCCAGGTCCC AGCGGCACCA ACATCATCAT TGGCTCCATC GCTGGGGCTG 6800
 TCCTGGTTGC AGCCATCGTC CTGGGCGGCA CGGGCTGGGG ATTTAAGTAA GAGACACACA 6860
 CACCCTGTGC CCCCTGGCAT CTTGAGGGG GGATCAGAAT CCCTACTGGT GGAGCTGAGG 6920
 GGGCCCTCCC TGAAAGCCCA ACTGAACCAG AGCTCACACG TCATAGGTCC AAGTAGCCTG 6980
 CAGGGCTTAA CATTTAGAAA CTAGGAGATT TTAGGCTAGA TGAGGTGCTC ACGCCTGTAA 7040
 TCCCAGCACT TTGGGAGGCC AAGGCAGGCG GATCACCTGA GGTGAGGAAT TCAAGACCAG 7100
 TCTGGCCAAC ATGGTGAAAC CCGTCTCTAT TAAAAATACA AAAATTAGCC AGCCATGGTG 7160
 GTGCACACCT GTAATCCCAG CTACTTGCGA GGCTGAGGCA GAGAATTGCT TGAACCCGGG 7220
 AGGTGGAGGT TGCAGTGAGC TGAGATCGCA CCATTGCACT CCAGCCTTGG GTGACAGAGC 7280
 AAGACTGCGT CAAAAAAAAA AAAAAAAAAA AAAAAAAGGA AAGAAAGAGA GAAAGAAAAG 7340
 AAAAGAGAAA AGAAATCAGG AGATTTTACA CTAGCAATTC GGATTTCCAG CTCTGGAAAC 7400
 ATGAAAAGGT TGAGCCCCAG CGTGCCTCTA AGCATCCCCA AATAGCCACA GAGTGGAGCT 7460



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 94 10 7487

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
P,X	<p>CANCER RESEARCH, vol. 53, 15 July 1993, MD US, pages 3382-3385, XP002036048 H.SAITO ET AL.: "Detailed deletion mapping of chromosome 17q in ovarian and breast cancers:2-cM region on 17q21.3 is often and commonly deleted in tumors" * the whole document *</p> <p>-----</p>	8-14	
			TECHNICAL FIELDS SEARCHED (Int.Cl.5)
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 31 July 1997	Examiner Cupido, M
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons</p> <p>----- & : member of the same patent family, corresponding document</p>			

EPO FORM 150 (03.92) (P04C01)

5 GGGCAGGGGC CACCCAAGCC AGGCATGTGT CCTCCAGTCT CCAGTTCCCA CCAGCCTATA 7520
 CTCCTTTTGTG CGTGTCTAAG TTTGGGGTCC TTGTGCCTGG TCTTACCCCC CTTAATGTGC 7580
 AGAGGGAGGA ACCCACGGCC CAAGGTCACA TGATTGAGTT AGTAGCAGAG TCAGAGCTGG 7640
 AACCAGGGACG CATTTTTTGTG GGTGCCCTGG GTAATTCTCC CTGGCCCTTA CATTAGTGTC 7700
 CAGGCCCCGG GGACCCCGGC CCCGCTCTGG GGCAAGGGGT CGCATGGCAG CCAAAGGCCC 7760
 CTCCCTGAGA GAAGCAAAAG GTCAGATGTC TCCTTTTCCT CTCCCCTTCC ACCATCCTCC 7820
 10 CCCTGCAGAA ACATTGCGCG AGGAAGGTAC GACCCGACCC AGCTGGGGGC AGTGTGATGC 7880
 CGGCCACGTC ATCCCTCCCG CTGTCCTTGT CTCCTCCATC TCATTGCTCA CCCGCGTTCT 7940
 GTTGATGGGG TGCGGGGCGG ATCCCACCCT GCGTGCCNNN NNNNNNNNNN ATCTGTTTTG 8000
 TCTTCCATAT CACCACTGTC TGACCTCCCG CAGATCCCTT CCCTGGCCAG CCTGTGACTT 8060
 GCCGCTGCC TCCAGGGCCC AGAACTGAGC TCCGGGGGCC TGCTGGGGGG CTCTCCCCGA 8120
 15 GGCCCCTGCT CACGTCCTCC CCTGATGCCC CCTCTCCGTT CCAGGTCCGG AGGGGCCTAA 8180
 GTGCCACCCT CCTCCCTCCA AGCCTGGCAC CCACCGTCTC GGCCCTGAAC CACGAGGCTG 8240
 CCCCCATCCA GCCACGGAGG GAGGCACCAT GCAAATGTCT TCCAGGTCCA AACCCTTCAA 8300
 CTCCTGGGTC CGCAGGGGTT TGGGTGGGGG CTGTGGCCCT GCCCTTGCCA CCACCAGGGT 8360
 20 GGACCAGGCC TGGAGGGCAC TTCCTCCACA GTCCCCCACC CACCTCCTGC GGCTCAGCCT 8420
 TGCACACCCA CTGCCCCGTG TGAATGTAGC TTCCACCTCA TGGATTGCCA CAGCTCAACT 8480
 CGGGGGCACC TGGAGGGATG CCCCCAGGCA GCCACCAGTG GACCTAGCCT GGATGGCCCC 8540
 TCCTTGCAAC CAGGCAGCTG AGACCAGGGT CTTATCTCTC TGGGACCTAG GGGGACGGGG 8600
 25 CTGACATCTA CATTTTTTAA AACTGAATCT TAATCGATGA ATGTAAACTC GGGGGTGCTG 8660
 GGGCCAGGGC AGATGTGGGG ATGTTTTGAC ATTTACAGGA GGCCCCGGAG AAAGTGAAGT 8720
 ATGGCCATGC CCTAGACCCT CCCCAGGAT GACCACACCC GAAGTCCTGT CACTGAGCAC 8780
 AGTCAGGGGC TGGGCATCCC AGCTTGCCCC CGCTTAGCCC CGCTGAGCTT GGAGGAAGTA 8840
 30 TGAGTGCTGA TTCAAACCAA AGCTGCCTGT GCCATGCCCA AGGCCTAGGT TATGGGTACG 8900
 GCAACCACAT GTCCCAGATC GTCTCCAATT CGAAAAACAAC CGTCCTGCTG TCCCTGTCAG 8960
 GACACATGGA TTTTGGCAGG GCGGGGGGGG GTTCTAGAAA ATATAGGTTT CTATAATAAA 9020
 ATGGCACCTT CCCCCTTTNN NNNNNNNNNN NNNGGGATAC CTCTGAATAT GGGTATCTGG 9080
 35 GGCTGGATAT GGGTGGGACA TGAGACTTCC TGTGACCAGC CACCCTGGCT CCCAGCTCTC 9140
 TGTATCCTCC TGCCCCGCCC TGGGGGGTGC CTACCCTGGN AGAACCAGG GAGGAGTGGA 9200
 GGCTGCCTCT GCCTGGGCCT CCACACAGCA TCCTGACATA CGCCACCTGG GGTGGGGGTG 9260
 GGGAGGCAGG GCCAGGAG 9278

(2) INFORMATION FOR SEQ ID NO: 10:

(1) SEQUENCE CHARACTERISTICS

(A) LENGTH: 17 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

GCACCTGCCC CGGCAGT 17

(2) INFORMATION FOR SEQ ID NO: 11:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 20 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

CCAGGACAGC CCCAGCGATG 20

(2) INFORMATION FOR SEQ ID NO: 12:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 22 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

GGCTGCTGAT CGCTTCTGCT AC 22

(2) INFORMATION FOR SEQ ID NO: 13:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 20 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

10

GAGAAGCTGA ATGTGGAGGG 20

(2) INFORMATION FOR SEQ ID NO: 14:

(i) SEQUENCE CHARACTERISTICS

15

(A) LENGTH: 19 base pairs

(B) TYPE: nucleic acid

20

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

GTCAGAGCCG TCCGCCAGC 19

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(2) INFORMATION FOR SEQ ID NO: 15:

(i) SEQUENCE CHARACTERISTICS

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(A) LENGTH: 22 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

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(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

45

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

GCCATCCTCC ACATAGCTCA GG 22

50

55

(2) INFORMATION FOR SEQ ID NO: 16:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 26 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

GATGTAAGTC AAGTTCCCAT CAGAGA 26

(2) INFORMATION FOR SEQ ID NO: 17:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 25 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

AACAGCTGGT GGTCGTTGAT CACAA 25

(2) INFORMATION FOR SEQ ID NO: 18:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 20 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

ATGAGGCTGC TCGGCGCTG 20

(2) INFORMATION FOR SEQ ID NO: 19:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 27 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

CACAGATCTG GGGGCATATG CTCCTG 27

(2) INFORMATION FOR SEQ ID NO: 20:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 27 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20:

AACAAGCTTC TACTGATGTC TCCCACC 27

SEQUENCE LISTING

5 Reference: 61 826 / u6

 Date: May 13, 1994

10 (1) GENERAL INFORMATION:

 (i) APPLICANT:

 (A) NAME: (1) CANCER INSTITUTE

15 (2) EISAI CO., LTD.

 (B) STREET: (1) 37-1, Kamiikebururo 1-chome

 Toshima-ku

 (2) 6-10, Koishikawa 4-chome, Bunkyo-ku

20 (C) CITY: Tokyo

 (D) STATE:

 (E) COUNTRY: Japan

25 (ii) TITLE OF INVENTION: MDC PROTEINS AND DNAs ENCODING
 THE SAME

30 (iii) NUMBER OF SEQUENCES: 20

 (iv) COMPUTER READABLE FORM:

 (A) MEDIUM TYPE: Floppy disk

35 (B) COMPUTER: IBM PC compatible

 (C) OPERATING SYSTEM: PC-DOS/MS-DOS

 (D) SOFTWARE: PatentIn Release #1.0, Version #1.25 (EPO)

40

 (2) INFORMATION FOR SEQ ID NO: 1:

 (i) SEQUENCE CHARACTERISTICS:

45 (A) LENGTH: 488 amino acids

 (B) TYPE: amino acid

 (D) TOPOLOGY: linear

50 (ii) MOLECULAR TYPE: protein

 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

55

Leu Leu Ser Ser Gln Tyr Val Glu Arg His Phe Ser Arg Glu Gly Thr
 1 5 10 15
 5 Thr Gln His Ser Thr Gly Ala Gly Asp His Cys Tyr Tyr Gln Gly Lys
 20 25 30
 Leu Arg Gly Asn Pro His Ser Phe Ala Ala Leu Ser Thr Cys Gln Gly
 35 40 45
 10 Leu His Gly Val Phe Ser Asp Gly Asn Leu Thr Tyr Ile Val Glu Pro
 50 55 60
 Gln Glu Val Ala Gly Pro Trp Gly Ala Pro Gln Gly Pro Leu Pro His
 65 70 75 80
 15 Leu Ile Tyr Arg Thr Pro Leu Leu Pro Asp Pro Leu Gly Cys Arg Glu
 85 90 95
 Pro Gly Cys Leu Phe Ala Val Pro Ala Gln Ser Ala Pro Pro Asn Arg
 100 105 110
 20 Pro Arg Leu Arg Arg Lys Arg Gln Val Arg Arg Gly His Pro Thr Val
 115 120 125
 25 His Ser Glu Thr Lys Tyr Val Glu Leu Ile Val Ile Asn Asp His Gln
 130 135 140
 Leu Phe Glu Gln Met Arg Gln Ser Val Val Leu Thr Ser Asn Phe Ala
 145 150 155 160
 30 Lys Ser Val Val Asn Leu Ala Asp Val Ile Tyr Lys Glu Gln Leu Asn
 165 170 175
 Thr Arg Ile Val Leu Val Ala Met Glu Thr Trp Ala Asp Gly Asp Lys
 180 185 190
 35 Ile Gln Val Gln Asp Asp Leu Leu Glu Thr Leu Ala Arg Leu Met Val
 195 200 205
 Tyr Arg Arg Glu Gly Leu Pro Glu Pro Ser Asn Ala Thr His Leu Phe
 210 215 220
 40 Ser Gly Arg Thr Phe Gln Ser Thr Ser Ser Gly Ala Ala Tyr Val Gly
 225 230 235 240
 45 Gly Ile Cys Ser Leu Ser His Gly Gly Gly Val Asn Glu Tyr Gly Asn
 245 250 255
 Met Gly Ala Met Ala Val Thr Leu Ala Gln Thr Leu Gly Gln Asn Leu
 260 265 270
 50 Gly Met Met Trp Asn Lys His Arg Ser Ser Ala Gly Asp Cys Lys Cys

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275 280 285
 Pro Asp Ile Trp Leu Gly Cys Ile Met Glu Asp Thr Gly Phe Tyr Leu
 290 295 300
 5 Pro Arg Lys Phe Ser Arg Cys Ser Ile Asp Glu Tyr Asn Gln Phe Leu
 305 310 315 320
 Gln Glu Gly Gly Gly Ser Cys Leu Phe Asn Lys Pro Leu Lys Leu Leu
 10 325 330 335
 Asp Pro Pro Glu Cys Gly Asn Gly Phe Val Glu Ala Gly Glu Glu Cys
 340 345 350
 15 Asp Cys Gly Ser Val Gln Glu Cys Ser Arg Ala Gly Gly Asn Cys Cys
 355 360 365
 Lys Lys Cys Thr Leu Thr His Asp Ala Met Cys Ser Asp Gly Leu Cys
 370 375 380
 20 Cys Arg Arg Cys Lys Tyr Glu Pro Arg Gly Val Ser Cys Arg Glu Ala
 385 390 395 400
 Val Asn Glu Cys Asp Ile Ala Glu Thr Cys Thr Gly Asp Ser Ser Gln
 405 410 415
 25 Cys Pro Pro Asn Leu His Lys Leu Asp Gly Tyr Tyr Cys Asp His Glu
 420 425 430
 Gln Gly Arg Cys Tyr Gly Gly Arg Cys Lys Thr Arg Asp Arg Gln Cys
 30 435 440 445
 Gln Val Leu Trp Gly His Ala Ala Ala Asp Arg Phe Cys Tyr Glu Lys
 450 455 460
 35 Leu Asn Val Glu Gly Thr Glu Arg Gly Ser Cys Gly Arg Lys Gly Ser
 465 470 475 480
 Gly Trp Val Gln Cys Ser Lys Gln
 485 488
 40

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 524 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULAR TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

(ii) MOLECULAR TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

5

Met Cys Trp Leu Ser His Gln Leu Leu Ser Ser Gln Tyr Val Glu Arg

1 5 10 15

His Phe Ser Arg Glu Gly Thr Thr Gln His Ser Thr Gly Ala Gly Asp

10

20 25 30

His Cys Tyr Tyr Gln Gly Lys Leu Arg Gly Asn Pro His Ser Phe Ala

35 40 45

Ala Leu Ser Thr Cys Gln Gly Leu His Gly Val Phe Ser Asp Gly Asn

15

50 55 60

Leu Thr Tyr Ile Val Glu Pro Gln Glu Val Ala Gly Pro Trp Gly Ala

65 70 75 80

Pro Gln Gly Pro Leu Pro His Leu Ile Tyr Arg Thr Pro Leu Leu Pro

20

85 90 95

Asp Pro Leu Gly Cys Arg Glu Pro Gly Cys Leu Phe Ala Val Pro Ala

100 105 110

Gln Ser Ala Pro Pro Asn Arg Pro Arg Leu Arg Arg Lys Arg Gln Val

25

115 120 125

Arg Arg Gly His Pro Thr Val His Ser Glu Thr Lys Tyr Val Glu Leu

30

130 135 140

Ile Val Ile Asn Asp His Gln Leu Phe Glu Gln Met Arg Gln Ser Val

145 150 155 160

Val Leu Thr Ser Asn Phe Ala Lys Ser Val Val Asn Leu Ala Asp Val

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165 170 175

Ile Tyr Lys Glu Gln Leu Asn Thr Arg Ile Val Leu Val Ala Met Glu

180 185 190

Thr Trp Ala Asp Gly Asp Lys Ile Gln Val Gln Asp Asp Leu Leu Glu

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195 200 205

Thr Leu Ala Arg Leu Met Val Tyr Arg Arg Glu Gly Leu Pro Glu Pro

210 215 220

Ser Asn Ala Thr His Leu Phe Ser Gly Arg Thr Phe Gln Ser Thr Ser

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225 230 235 240

Ser Gly Ala Ala Tyr Val Gly Gly Ile Cys Ser Leu Ser His Gly Gly

245 250 255

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Gly Val Asn Glu Tyr Gly Asn Met Gly Ala Met Ala Val Thr Leu Ala

55

260 265 270
 Gln Thr Leu Gly Gln Asn Leu Gly Met Met Trp Asn Lys His Arg Ser
 5 275 280 285
 Ser Ala Gly Asp Cys Lys Cys Pro Asp Ile Trp Leu Gly Cys Ile Met
 290 295 300
 Glu Asp Thr Gly Phe Tyr Leu Pro Arg Lys Phe Ser Arg Cys Ser Ile
 10 305 310 315 320
 Asp Glu Tyr Asn Gln Phe Leu Gln Glu Gly Gly Gly Ser Cys Leu Phe
 325 330 335
 15 Asn Lys Pro Leu Lys Leu Leu Asp Pro Pro Glu Cys Gly Asn Gly Phe
 340 345 350
 Val Glu Ala Gly Glu Glu Cys Asp Cys Gly Ser Val Gln Glu Cys Ser
 355 360 365
 20 Arg Ala Gly Gly Asn Cys Cys Lys Lys Cys Thr Leu Thr His Asp Ala
 370 375 380
 Met Cys Ser Asp Gly Leu Cys Cys Arg Arg Cys Lys Tyr Glu Pro Arg
 25 385 390 395 400
 Gly Val Ser Cys Arg Glu Ala Val Asn Glu Cys Asp Ile Ala Glu Thr
 405 410 415
 Cys Thr Gly Asp Ser Ser Gln Cys Pro Pro Asn Leu His Lys Leu Asp
 30 420 425 430
 Gly Tyr Tyr Cys Asp His Glu Gln Gly Arg Cys Tyr Gly Gly Arg Cys
 435 440 445
 35 Lys Thr Arg Asp Arg Gln Cys Gln Val Leu Trp Gly His Ala Ala Ala
 450 455 460
 Asp Arg Phe Cys Tyr Glu Lys Leu Asn Val Glu Gly Thr Glu Arg Gly
 465 470 475 480
 40 Ser Cys Gly Arg Lys Gly Ser Gly Trp Val Gln Cys Ser Lys Gln Asp
 485 490 495
 Val Leu Cys Gly Phe Leu Leu Cys Val Asn Ile Ser Gly Ala Pro Arg
 500 505 510
 45 Leu Gly Asp Leu Val Gly Asp Ile Ser Ser Val Thr Phe Tyr His Gln
 515 520 525
 Gly Lys Glu Leu Asp Cys Arg Gly Gly His Val Gln Leu Ala Asp Gly
 50 530 535 540
 Ser Asp Leu Ser Tyr Val Glu Asp Gly Thr Ala Cys Gly Pro Asn Met

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Met Cys Trp Leu Ser His Gln Leu Leu Ser Ser Gln Tyr Val Glu Arg
 1 5 10 15
 5 His Phe Ser Arg Glu Gly Thr Thr Gln His Ser Thr Gly Ala Gly Asp
 20 25 30
 His Cys Tyr Tyr Gln Gly Lys Leu Arg Gly Asn Pro His Ser Phe Ala
 35 40 45
 10 Ala Leu Ser Thr Cys Gln Gly Leu His Gly Val Phe Ser Asp Gly Asn
 50 55 60
 Leu Thr Tyr Ile Val Glu Pro Gln Glu Val Ala Gly Pro Trp Gly Ala
 65 70 75 80
 15 Pro Gln Gly Pro Leu Pro His Leu Ile Tyr Arg Thr Pro Leu Leu Pro
 85 90 95
 Asp Pro Leu Gly Cys Arg Glu Pro Gly Cys Leu Phe Ala Val Pro Ala
 100 105 110
 20 Gln Ser Ala Pro Pro Asn Arg Pro Arg Leu Arg Arg Lys Arg Gln Val
 115 120 125
 Arg Arg Gly His Pro Thr Val His Ser Glu Thr Lys Tyr Val Glu Leu
 130 135 140
 25 Ile Val Ile Asn Asp His Gln Leu Phe Glu Gln Met Arg Gln Ser Val
 145 150 155 160
 30 Val Leu Thr Ser Asn Phe Ala Lys Ser Val Val Asn Leu Ala Asp Val
 165 170 175
 Ile Tyr Lys Glu Gln Leu Asn Thr Arg Ile Val Leu Val Ala Met Glu
 180 185 190
 35 Thr Trp Ala Asp Gly Asp Lys Ile Gln Val Gln Asp Asp Leu Leu Glu
 195 200 205
 Thr Leu Ala Arg Leu Met Val Tyr Arg Arg Glu Gly Leu Pro Glu Pro
 210 215 220
 40 Ser Asn Ala Thr His Leu Phe Ser Gly Arg Thr Phe Gln Ser Thr Ser
 225 230 235 240
 Ser Gly Ala Ala Tyr Val Gly Gly Ile Cys Ser Leu Ser His Gly Gly
 245 250 255
 45 Gly Val Asn Glu Tyr Gly Asn Met Gly Ala Met Ala Val Thr Leu Ala
 260 265 270
 Gln Thr Leu Gly Gln Asn Leu Gly Met Met Trp Asn Lys His Arg Ser
 275 280 285
 50
 55

Ser Ala Gly Asp Cys Lys Cys Pro Asp Ile Trp Leu Gly Cys Ile Met
 290 295 300
 5 Glu Asp Thr Gly Phe Tyr Leu Pro Arg Lys Phe Ser Arg Cys Ser Ile
 305 310 315 320
 Asp Glu Tyr Asn Gln Phe Leu Gln Glu Gly Gly Gly Ser Cys Leu Phe
 325 330 335
 10 Asn Lys Pro Leu Lys Leu Leu Asp Pro Pro Glu Cys Gly Asn Gly Phe
 340 345 350
 Val Glu Ala Gly Glu Glu Cys Asp Cys Gly Ser Val Gln Glu Cys Ser
 355 360 365
 15 Arg Ala Gly Gly Asn Cys Cys Lys Lys Cys Thr Leu Thr His Asp Ala
 370 375 380
 Met Cys Ser Asp Gly Leu Cys Cys Arg Arg Cys Lys Tyr Glu Pro Arg
 20 385 390 395 400
 Gly Val Ser Cys Arg Glu Ala Val Asn Glu Cys Asp Ile Ala Glu Thr
 405 410 415
 25 Cys Thr Gly Asp Ser Ser Gln Cys Pro Pro Asn Leu His Lys Leu Asp
 420 425 430
 Gly Tyr Tyr Cys Asp His Glu Gln Gly Arg Cys Tyr Gly Gly Arg Cys
 435 440 445
 30 Lys Thr Arg Asp Arg Gln Cys Gln Val Leu Trp Gly His Ala Ala Ala
 450 455 460
 Asp Arg Phe Cys Tyr Glu Lys Leu Asn Val Glu Gly Thr Glu Arg Gly
 465 470 475 480
 35 Ser Cys Gly Arg Lys Gly Ser Gly Trp Val Gln Cys Ser Lys Gln Pro
 485 490 495
 Gln Gln Gly Arg Ala Val Trp Leu Pro Pro Leu Cys Gln His Leu Trp
 500 505 510
 40 Ser Ser Ser Ala Arg Gly Pro Gly Gly Arg His Gln
 515 520 524

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 670 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

545 550 555 560
 Leu Cys Leu Asp His Arg Cys Leu Pro Ala Ser Ala Phe Asn Phe Ser
 5 565 570 575
 Thr Cys Pro Gly Ser Gly Glu Arg Arg Ile Cys Ser His His Gly Val
 580 585 590
 Cys Ser Asn Glu Gly Lys Cys Ile Cys Gln Pro Asp Trp Thr Gly Lys
 10 595 600 605
 Asp Cys Ser Ile His Asn Pro Leu Pro Thr Ser Pro Pro Thr Gly Glu
 610 615 620
 Thr Glu Arg Tyr Lys Gly Pro Ser Gly Thr Asn Ile Ile Ile Gly Ser
 15 625 630 635 640
 Ile Ala Gly Ala Val Leu Val Ala Ala Ile Val Leu Gly Gly Thr Gly
 645 650 655
 Trp Gly Phe Lys Asn Ile Arg Arg Gly Arg Ser Gly Gly Ala
 20 660 665 670

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 769 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULAR TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

35 Met Arg Leu Leu Arg Arg Trp Ala Phe Ala Ala Leu Leu Leu Ser Leu
 1 5 10 15
 Leu Pro Thr Pro Gly Leu Gly Thr Gln Gly Pro Ala Gly Ala Leu Arg
 20 25 30
 Trp Gly Gly Leu Pro Gln Leu Gly Gly Pro Gly Ala Pro Glu Val Thr
 35 40 45
 Glu Pro Ser Arg Leu Val Arg Glu Ser Ser Gly Gly Glu Val Arg Lys
 45 50 55 60
 Gln Gln Leu Asp Thr Arg Val Arg Gln Glu Pro Pro Gly Gly Pro Pro
 65 70 75 80
 Val His Leu Ala Gln Val Ser Phe Val Ile Pro Ala Phe Asn Ser Asn
 50 85 90 95

55

	Phe Thr Leu Asp Leu Glu Leu Asn His His Leu Leu Ser Ser Gln Tyr	
	100	105 110
5	Val Glu Arg His Phe Ser Arg Glu Gly Thr Thr Gln His Ser Thr Gly	
	115	120 125
	Ala Gly Asp His Cys Tyr Tyr Gln Gly Lys Leu Arg Gly Asn Pro His	
	130	135 140
10	Ser Phe Ala Ala Leu Ser Thr Cys Gln Gly Leu His Gly Val Phe Ser	
	145	150 155 160
	Asp Gly Asn Leu Thr Tyr Ile Val Glu Pro Gln Glu Val Ala Gly Pro	
	165	170 175
15	Trp Gly Ala Pro Gln Gly Pro Leu Pro His Leu Ile Tyr Arg Thr Pro	
	180	185 190
	Leu Leu Pro Asp Pro Leu Gly Cys Arg Glu Pro Gly Cys Leu Phe Ala	
20	195	200 205
	Val Pro Ala Gln Ser Ala Pro Pro Asn Arg Pro Arg Leu Arg Arg Lys	
	210	215 220
25	Arg Gln Val Arg Arg Gly His Pro Thr Val His Ser Glu Thr Lys Tyr	
	225	230 235 240
	Val Glu Leu Ile Val Ile Asn Asp His Gln Leu Phe Glu Gln Met Arg	
	245	250 255
30	Gln Ser Val Val Leu Thr Ser Asn Phe Ala Lys Ser Val Val Asn Leu	
	260	265 270
	Ala Asp Val Ile Tyr Lys Glu Gln Leu Asn Thr Arg Ile Val Leu Val	
	275	280 285
35	Ala Met Glu Thr Trp Ala Asp Gly Asp Lys Ile Gln Val Gln Asp Asp	
	290	295 300
	Leu Leu Glu Thr Leu Ala Arg Leu Met Val Tyr Arg Arg Glu Gly Leu	
40	305	310 315 320
	Pro Glu Pro Ser Asn Ala Thr His Leu Phe Ser Gly Arg Thr Phe Gln	
	325	330 335
45	Ser Thr Ser Ser Gly Ala Ala Tyr Val Gly Gly Ile Cys Ser Leu Ser	
	340	345 350
	His Gly Gly Gly Val Asn Glu Tyr Gly Asn Met Gly Ala Met Ala Val	
	355	360 365
50	Thr Leu Ala Gln Thr Leu Gly Gln Asn Leu Gly Met Met Trp Asn Lys	
	370	375 380

55

	35	40	45	
	CTG CAT GGG GTC TTC TCT GAT GGG AAC TTG ACT TAC ATC GTG GAG CCC			192
5	Leu His Gly Val Phe Ser Asp Gly Asn Leu Thr Tyr Ile Val Glu Pro			
	50	55	60	
	CAA GAG GTG GCT GGA CCT TGG GGA GCC CCT CAG GGA CCC CTT CCC CAC			240
	Gln Glu Val Ala Gly Pro Trp Gly Ala Pro Gln Gly Pro Leu Pro His			
10	65	70	75	80
	CTC ATT TAC CGG ACC CCT CTC CTC CCA GAT CCC CTC GGA TGC AGG GAA			288
	Leu Ile Tyr Arg Thr Pro Leu Leu Pro Asp Pro Leu Gly Cys Arg Glu			
	85	90	95	
15	CCA GGC TGC CTG TTT GCT GTG CCT GCC CAG TCG GCT CCT CCA AAC CGG			336
	Pro Gly Cys Leu Phe Ala Val Pro Ala Gln Ser Ala Pro Pro Asn Arg			
	100	105	110	
20	CCG AGG CTG AGA AGG AAA AGG CAG GTC CGC CGG GGC CAC CCT ACA GTG			384
	Pro Arg Leu Arg Arg Lys Arg Gln Val Arg Arg Gly His Pro Thr Val			
	115	120	125	
25	CAC AGT GAA ACC AAG TAT GTG GAG CTA ATT GTG ATC AAC GAC CAC CAG			432
	His Ser Glu Thr Lys Tyr Val Glu Leu Ile Val Ile Asn Asp His Gln			
	130	135	140	
	CTG TTC GAG CAG ATG CGA CAG TCG GTG GTC CTC ACC AGC AAC TTT GCC			480
30	Leu Phe Glu Gln Met Arg Gln Ser Val Val Leu Thr Ser Asn Phe Ala			
	145	150	155	160
	AAG TCC GTG GTG AAC CTG GCC GAT GTG ATA TAC AAG GAG CAG CTC AAC			528
	Lys Ser Val Val Asn Leu Ala Asp Val Ile Tyr Lys Glu Gln Leu Asn			
35	165	170	175	
	ACT CGC ATC GTC CTG GTT GCC ATG GAA ACA TGG GCA GAT GGG GAC AAG			576
	Thr Arg Ile Val Leu Val Ala Met Glu Thr Trp Ala Asp Gly Asp Lys			
	180	185	190	
40	ATC CAG GTG CAG GAT GAC CTC CTG GAG ACC CTG GCC CGG CTC ATG GTC			624
	Ile Gln Val Gln Asp Asp Leu Leu Glu Thr Leu Ala Arg Leu Met Val			
	195	200	205	
45	TAC CGA CGG GAG GGT CTG CCT GAG CCC AGT AAT GCC ACC CAC CTC TTC			672
	Tyr Arg Arg Glu Gly Leu Pro Glu Pro Ser Asn Ala Thr His Leu Phe			
	210	215	220	
50	TCG GGC AGG ACC TTC CAG AGC ACG AGC AGC GGG GCA GCC TAC GTG GGG			720
	Ser Gly Arg Thr Phe Gln Ser Thr Ser Ser Gly Ala Ala Tyr Val Gly			

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EP 0 633 268 A2

	225		230		235		240	
	GGC ATA TGC TCC CTG TCC CAT GGC GGG GGT GTG AAC GAG TAC GGC AAC							768
	Gly Ile Cys Ser Leu Ser His Gly Gly Gly Val Asn Glu Tyr Gly Asn							
5			245		250		255	
	ATG GGG GCG ATG GCC GTG ACC CTT GCC CAG ACG CTG GGA CAG AAC CTG							816
	Met Gly Ala Met Ala Val Thr Leu Ala Gln Thr Leu Gly Gln Asn Leu							
10			260		265		270	
	GGC ATG ATG TGG AAC AAA CAC CGG AGC TCG GCA GGG GAC TGC AAG TGT							864
	Gly Met Met Trp Asn Lys His Arg Ser Ser Ala Gly Asp Cys Lys Cys							
15			275		280		285	
	CCA GAC ATC TGG CTG GGC TGC ATC ATG GAG GAC ACT GGG TTC TAC CTG							912
	Pro Asp Ile Trp Leu Gly Cys Ile Met Glu Asp Thr Gly Phe Tyr Leu							
20			290		295		300	
	CCC CGC AAG TTC TCT CGC TGC AGC ATC GAC GAG TAC AAC CAG TTT CTG							960
	Pro Arg Lys Phe Ser Arg Cys Ser Ile Asp Glu Tyr Asn Gln Phe Leu							
25			305		310		315	
	CAG GAG GGT GGT GGC AGC TGC CTC TTC AAC AAG CCC CTC AAG CTC CTG							1008
	Gln Glu Gly Gly Gly Ser Cys Leu Phe Asn Lys Pro Leu Lys Leu Leu							
30			325		330		335	
	GAC CCC CCA GAG TGC GGG AAC GGC TTC GTG GAG GCA GGG GAG GAG TGC							1056
	Asp Pro Pro Glu Cys Gly Asn Gly Phe Val Glu Ala Gly Glu Glu Cys							
35			340		345		350	
	GAC TGC GGC TCG GTG CAG GAG TGC AGC CGC GCA GGT GGC AAC TGC TGC							1104
	Asp Cys Gly Ser Val Gln Glu Cys Ser Arg Ala Gly Gly Asn Cys Cys							
40			355		360		365	
	AAG AAA TGC ACC CTG ACT CAC GAC GCC ATG TGC AGC GAC GGG CTC TGC							1152
	Lys Lys Cys Thr Leu Thr His Asp Ala Met Cys Ser Asp Gly Leu Cys							
45			370		375		380	
	TGT CGC CGC TGC AAG TAC GAA CCA CGG GGT GTG TCc TGC CGA GAG GCC							1200
	Cys Arg Arg Cys Lys Tyr Glu Pro Arg Gly Val Ser Cys Arg Glu Ala							
50			385		390		395	
	GTG AAC GAG TGC GAC ATC GCG GAG ACC TGC ACC GGG GAC TCT AGC CAG							1248
	Val Asn Glu Cys Asp Ile Ala Glu Thr Cys Thr Gly Asp Ser Ser Gln							
55			405		410		415	
	TGC CCG CCT AAC CTG CAC AAG CTG GAC GGT TAC TAC TGT GAC CAT GAG							1296
	Cys Pro Pro Asn Leu His Lys Leu Asp Gly Tyr Tyr Cys Asp His Glu							

	420	425	430	
	CAG GGC CGC TGC TAC GGA GGT CGC TGC AAA ACC CGG GAC CGG CAG TGC			1344
5	Gln Gly Arg Cys Tyr Gly Gly Arg Cys Lys Thr Arg Asp Arg Gln Cys			
	435	440	445	
	CAG GTT CTT TGG GGC CAT GCG GCT GCT GAT CGC TTC TGC TAC GAG AAG			1392
10	Gln Val Leu Trp Gly His Ala Ala Ala Asp Arg Phe Cys Tyr Glu Lys			
	450	455	460	
	CTG AAT GTG GAG GGG ACG GAG CGT GGG AGC TGT GGG CGC AAG GGA TCC			1440
	Leu Asn Val Glu Gly Thr Glu Arg Gly Ser Cys Gly Arg Lys Gly Ser			
15	465	470	475	480
	GGC TGG GTC CAG TGC AGT AAG CAG			1464
	Gly Trp Val Gln Cys Ser Lys Gln			
20	485			

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:

- 25 (A) LENGTH: 2923 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDNESS: double
- 30 (D) TOPOLOGY: linear

(ii) MOLECULAR TYPE: cDNA to mRNA

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Homo sapiens

35 (vii) IMMEDIATE SOURCE:

- (A) LIBRARY: human fetal brain cDNA library

(ix) FEATURE:

- 40 (A) NAME/KEY: 5'UTR
- (B) LOCATION: 1..27

(ix) FEATURE:

- 45 (A) NAME/KEY: CDS
- (B) LOCATION: 28..1599

(ix) FEATURE:

- 50 (A) NAME/KEY: 3'UTR
- (B) LOCATION: 1600..2923

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

55

GCGTTTACTG GCAAACCGCA TTTGTAA ATG TGC TGG CTG AGC CAC CAA CTC 51
Met Cys Trp Leu Ser His Gln Leu

5 1 5
CTC TCC TCG CAA TAC GTG GAG CGC CAC TTC AGC CGG GAG GGG ACA ACC 99
Leu Ser Ser Gln Tyr Val Glu Arg His Phe Ser Arg Glu Gly Thr Thr

10 10 20
CAG CAC AGC ACC GGG GCT GGA GAC CAC TGC TAC TAC CAG GGG AAG CTC 147
Gln His Ser Thr Gly Ala Gly Asp His Cys Tyr Tyr Gln Gly Lys Leu

15 25 30 35 40
CGG GGG AAC CCG CAC TCC TTC GCC GCC CTC TCC ACC TGC CAG GGG CTG 195
Arg Gly Asn Pro His Ser Phe Ala Ala Leu Ser Thr Cys Gln Gly Leu

20 45 50 55
CAT GGG GTC TTC TCT GAT GGG AAC TTG ACT TAC ATC GTG GAG CCC CAA 243
His Gly Val Phe Ser Asp Gly Asn Leu Thr Tyr Ile Val Glu Pro Gln

25 60 65 70
GAG GTG GCT GGA CCT TGG GGA GCC CCT CAG GGA CCC CTT CCC CAC CTC 291
Glu Val Ala Gly Pro Trp Gly Ala Pro Gln Gly Pro Leu Pro His Leu

30 75 80 85
ATT TAC CGG ACC CCT CTC CTC CCA GAT CCC CTC GGA TGC AGG GAA CCA 339
Ile Tyr Arg Thr Pro Leu Leu Pro Asp Pro Leu Gly Cys Arg Glu Pro

35 90 95 100
GGC TGC CTG TTT GCT GTG CCT GCC CAG TCG GCT CCT CCA AAC CGG CCG 387
Gly Cys Leu Phe Ala Val Pro Ala Gln Ser Ala Pro Pro Asn Arg Pro

40 105 110 115 120
AGG CTG AGA AGG AAA AGG CAG GTC CGC CGG GGC CAC CCT ACA GTG CAC 435
Arg Leu Arg Arg Lys Arg Gln Val Arg Arg Gly His Pro Thr Val His

45 125 130 135
AGT GAA ACC AAG TAT GTG GAG CTA ATT GTG ATC AAC GAC CAC CAG CTG 483
Ser Glu Thr Lys Tyr Val Glu Leu Ile Val Ile Asn Asp His Gln Leu

50 140 145 150
TTC GAG CAG ATG CGA CAG TCG GTG GTC CTC ACC AGC AAC TTT GCC AAG 531
Phe Glu Gln Met Arg Gln Ser Val Val Leu Thr Ser Asn Phe Ala Lys

55 155 160 165
TCC GTG GTG AAC CTG GCC GAT GTG ATA TAC AAG GAG CAG CTC AAC ACT 579
Ser Val Val Asn Leu Ala Asp Val Ile Tyr Lys Glu Gln Leu Asn Thr

170 175 180

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Asn Phe Ser Thr Cys Pro Gly Ser Gly Glu Arg Arg Ile Cys Ser His
675 680 685
5 His Gly Val Cys Ser Asn Glu Gly Lys Cys Ile Cys Gln Pro Asp Trp
690 695 700
Thr Gly Lys Asp Cys Ser Ile His Asn Pro Leu Pro Thr Ser Pro Pro
705 710 715 720
10 Thr Gly Glu Thr Glu Arg Tyr Lys Gly Pro Ser Gly Thr Asn Ile Ile
725 730 735
Ile Gly Ser Ile Ala Gly Ala Val Leu Val Ala Ala Ile Val Leu Gly
740 745 750
15 Gly Thr Gly Trp Gly Phe Lys Asn Ile Arg Arg Gly Arg Ser Gly Gly
755 760 765
Ala
20 769

(2) INFORMATION FOR SEQ ID NO: 5:

- (i) SEQUENCE CHARACTERISTICS:
25 (A) LENGTH: 1464 base pairs
(B) TYPE: nucleic acid
(C) STRANDNESS: double
30 (D) TOPOLOGY: linear
(ii) MOLECULAR TYPE: cDNA to mRNA
(xi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens
35 (vii) IMMEDIATE SOURCE:
(A) LIBRARY: human fetal brain cDNA library
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

40 CTC CTC TCC TCG CAA TAC GTG GAG CGC CAC TTC AGC CGG GAG GGG ACA 48
Leu Leu Ser Ser Gln Tyr Val Glu Arg His Phe Ser Arg Glu Gly Thr
1 5 10 15
45 ACC CAG CAC AGC ACC GGG GCT GGA GAC CAC TGC TAC TAC CAG GGG AAG 96
Thr Gln His Ser Thr Gly Ala Gly Asp His Cys Tyr Tyr Gln Gly Lys
20 25 30
50 CTC CGG GGG AAC CCG CAC TCC TTC GCC GCC CTC TCC ACC TGC CAG GGG 144
Leu Arg Gly Asn Pro His Ser Phe Ala Ala Leu Ser Thr Cys Gln Gly

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AAA TGC ACC CTG ACT CAC GAC GCC ATG TGC AGC GAC GGG CTC TGC TGT 1203
 Lys Cys Thr Leu Thr His Asp Ala Met Cys Ser Asp Gly Leu Cys Cys
 380 385 390
 5 CGC CGC TGC AAG TAC GAA CCA CGG GGT GTG TCc TGC CGA GAG GCC GTG 1251
 Arg Arg Cys Lys Tyr Glu Pro Arg Gly Val Ser Cys Arg Glu Ala Val
 395 400 405
 10 AAC GAG TGC GAC ATC GCG GAG ACC TGC ACC GGG GAC TCT AGC CAG TGC 1299
 Asn Glu Cys Asp Ile Ala Glu Thr Cys Thr Gly Asp Ser Ser Gln Cys
 410 415 420
 15 CCG CCT AAC CTG CAC AAG CTG GAC GGT TAC TAC TGT GAC CAT GAG CAG 1347
 Pro Pro Asn Leu His Lys Leu Asp Gly Tyr Tyr Cys Asp His Glu Gln
 425 430 435 440
 GGC CGC TGC TAC GGA GGT CGC TGC AAA ACC CGG GAC CGG CAG TGC CAG 1395
 20 Gly Arg Cys Tyr Gly Gly Arg Cys Lys Thr Arg Asp Arg Gln Cys Gln
 445 450 455
 GTT CTT TGG GGC CAT GCG GCT GCT GAT CGC TTC TGC TAC GAG AAG CTG 1443
 Val Leu Trp Gly His Ala Ala Ala Asp Arg Phe Cys Tyr Glu Lys Leu
 25 460 465 470
 AAT GTG GAG GGG ACG GAG CGT GGG AGC TGT GGG CGC AAG GGA TCC GGC 1491
 Asn Val Glu Gly Thr Glu Arg Gly Ser Cys Gly Arg Lys Gly Ser Gly
 30 475 480 485
 TGG GTC CAG TGC AGT AAG CAG CCC CAA CAG GGA CGT GCT GTG TGG CTT 1539
 Trp Val Gln Cys Ser Lys Gln Pro Gln Gln Gly Arg Ala Val Trp Leu
 490 495 500
 35 CCT CCT CTG TGT CAA CAT CTC TGG AGC TCC TCG GCT AGG GGA CCT GGT 1587
 Pro Pro Leu Cys Gln His Leu Trp Ser Ser Ser Ala Arg Gly Pro Gly
 505 510 515 520
 40 GGG AGA CAT CAG TAGTGTCACC TTCTACCACC AGGGCAAGGA GCTGGACTGC 1639
 Gly Arg His Gln
 AGGGGAGGCC ACGTGCAGCT GGCGGACGGC TCTGACCTGA GCTATGTGGA GGATGGCACA 1699
 GCCTGCGGGC CTAACATGTT GTGCCTGGAC CATCGCTGCC TGCCAGCTTC TGCCTTCAAC 1759
 45 TTCAGCACCT GCCCCGGCAG TGGGGAGCGC CGGATTGTCT CCCACCACGG GGTCTGCAGC 1819
 AATGAAGGGA AGTGCATCTG TCAGCCAGAC TGGACAGGCA AAGACTGCAG TATCCATAAC 1879
 CCCCTGCCCCA CGTCCCCACC CACGGGGGAG ACGGAGAGAT ATAAAGGTCC CAGCGGCACC 1939
 AACATCATCA TTGGCTCCAT CGCTGGGGCT GTCCTGGTTG CAGCCATCGT CCTGGGCGGC 1999
 50 ACGGGCTGGG GATTTAAAAA CATTCGCCGA GGAAGGTCCG GAGGGGCCTA AGTGCCACCC 2059

TCCTCCCTCC AAGCCTGGCA CCCACCGTCT CGGCCCTGAA CCACGAGGCT GCCCCCATCC 2119
 AGCCACGGAG GGAGGCACCA TGCAAATGTC TTCCAGGTCC AAACCCCTTCA ACTCCTGGCT 2179
 CCGCAGGGGT TTGGGTGGGG GCTGTGGCCC TGCCCTTGGC ACCACCAGGG TGGACCAGGC 2239
 CTGGAGGGCA CTTCTCCAC AGTCCCCCAC CCACCTCCTG CGGCTCAGCC TTGCACACCC 2299
 ACTGCCCCGT GTGAATGTAG CTTCCACCTC ATGGATTGCC ACAGCTCAAC TCGGGGGCAC 2359
 CTGGAGGGAT GCCCCCAGGC AGCCACCAGT GGACCTAGCC TGGATGGCCC CTCCTTGCAA 2419
 CCAGGCAGCT GAGACCAGGG TCTTATCTCT CTGGGACCTA GGGGGACGGG GCTGACATCT 2479
 ACATTTTITA AAAGTGAATC TTAATCGATG AATGTAAACT CGGGGGTGCT GGGGCCAGGG 2539
 CAGATGTGGG GATGTTTTGA CATTTACAGG AGGCCCCGGA GAAACTGAGG TATGGCCATG 2599
 CCCTAGACCC TCCCCAAGGA TGACCACACC CGAAGTCCTG TCACTGAGCA CAGTCAGGGG 2659
 CTGGGCATCC CAGCTTGCCC CCGCTTAGCC CCGCTGAGCT TGGAGGAAGT ATGAGTGCTG 2719
 ATTCAAACCA AAGCTGCCTG TGCCATGCCC AAGGCCTAGG TTATGGGTAC GGCAACCACA 2779
 TGTCCTCAGAT CGTCTCCAAT TCGAAAACAA CCGTCTTGCT GTCCCTGTCA GGACACATGG 2839
 ATTTTGGCAG GGCGGGGGGG GGTCTAGAA AATATAGGTT CCTATAATAA AATGGCACCT 2899
 TCCCCCTTTA AAAAAAAAAA AAAA 2923

(2) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 2913 base pairs

(B) TYPE: nucleic acid

(C) STRANDNESS: double

(D) TOPOLOGY: linear

(ii) MOLECULAR TYPE: cDNA to mRNA

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(vii) IMMEDIATE SOURCE:

(A) LIBRARY: human fetal brain cDNA library

(ix) FEATURE:

(A) NAME/KEY: 5'UTR

(B) LOCATION: 1..27

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 28..2037

(ix) FEATURE:

(A) NAME/KEY: 3'UTR

(B) LOCATION: 2038..2913

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

5	CGGTTTACTG GCAAACCGCA TTTGTAA ATG TGC TGG CTG AGC CAC CAA CTC	51
	Met Cys Trp Leu Ser His Gln Leu	
	1 5	
10	CTC TCC TCG CAA TAC GTG GAG CGC CAC TTC AGC CGG GAG GGG ACA ACC	99
	Leu Ser Ser Gln Tyr Val Glu Arg His Phe Ser Arg Glu Gly Thr Thr	
	10 15 20	
15	CAG CAC AGC ACC GGG GCT GGA GAC CAC TGC TAC TAC CAG GGG AAG CTC	147
	Gln His Ser Thr Gly Ala Gly Asp His Cys Tyr Tyr Gln Gly Lys Leu	
	25 30 35 40	
20	CGG GGG AAC CCG CAC TCC TTC GCC GCC CTC TCC ACC TGC CAG GGG CTG	195
	Arg Gly Asn Pro His Ser Phe Ala Ala Leu Ser Thr Cys Gln Gly Leu	
	45 50 55	
25	CAT GGG GTC TTC TCT GAT GGG AAC TTG ACT TAC ATC GTG GAG CCC CAA	243
	His Gly Val Phe Ser Asp Gly Asn Leu Thr Tyr Ile Val Glu Pro Gln	
	60 65 70	
30	GAG GTG GCT GGA CCT TGG GGA GCC CCT CAG GGA CCC CTT CCC CAC CTC	291
	Glu Val Ala Gly Pro Trp Gly Ala Pro Gln Gly Pro Leu Pro His Leu	
	75 80 85	
35	ATT TAC CGG ACC CCT CTC CTC CCA GAT CCC CTC GGA TGC AGG GAA CCA	339
	Ile Tyr Arg Thr Pro Leu Leu Pro Asp Pro Leu Gly Cys Arg Glu Pro	
	90 95 100	
40	GGC TGC CTG TTT GCT GTG CCT GCC CAG TCG GCT CCT CCA AAC CGG CCG	387
	Gly Cys Leu Phe Ala Val Pro Ala Gln Ser Ala Pro Pro Asn Arg Pro	
	105 110 115 120	
45	AGG CTG AGA AGG AAA AGG CAG GTC CGC CGG GGC CAC CCT ACA GTG CAC	435
	Arg Leu Arg Arg Lys Arg Gln Val Arg Arg Gly His Pro Thr Val His	
	125 130 135	
50	AGT GAA ACC AAG TAT GTG GAG CTA ATT GTG ATC AAC GAC CAC CAG CTG	483
	Ser Glu Thr Lys Tyr Val Glu Leu Ile Val Ile Asn Asp His Gln Leu	
	140 145 150	
55	TTC GAG CAG ATG CGA CAG TCG GTG GTC CTC ACC AGC AAC TTT GCC AAG	531
	Phe Glu Gln Met Arg Gln Ser Val Val Leu Thr Ser Asn Phe Ala Lys	
	155 160 165	
60	TCC GTG GTG AAC CTG GCC GAT GTG ATA TAC AAG GAG CAG CTC AAC ACT	579

	Ser Val Val Asn Leu Ala Asp Val Ile Tyr Lys Glu Gln Leu Asn Thr	
	170 175 180	
5	CGC ATC GTC CTG GTT GCC ATG GAA ACA TGG GCA GAT GGG GAC AAG ATC	627
	Arg Ile Val Leu Val Ala Met Glu Thr Trp Ala Asp Gly Asp Lys Ile	
	185 190 195 200	
	CAG GTG CAG GAT GAC CTC CTG GAG ACC CTG GCC CGG CTC ATG GTC TAC	675
10	Gln Val Gln Asp Asp Leu Leu Glu Thr Leu Ala Arg Leu Met Val Tyr	
	205 210 215	
	CGA CGG GAG GGT CTG CCT GAG CCC AGT AAT GCC ACC CAC CTC TTC TCG	723
15	Arg Arg Glu Gly Leu Pro Glu Pro Ser Asn Ala Thr His Leu Phe Ser	
	220 225 230	
	GGC AGG ACC TTC CAG AGC ACG AGC AGC GGG GCA GCC TAC GTG GGG GGC	771
	Gly Arg Thr Phe Gln Ser Thr Ser Ser Gly Ala Ala Tyr Val Gly Gly	
20	235 240 245	
	ATA TGC TCC CTG TCC CAT GGC GGG GGT GTG AAC GAG TAC GGC AAC ATG	819
	Ile Cys Ser Leu Ser His Gly Gly Gly Val Asn Glu Tyr Gly Asn Met	
25	250 255 260	
	GGG GCG ATG GCC GTG ACC CTT GCC CAG ACG CTG GGA CAG AAC CTG GGC	867
	Gly Ala Met Ala Val Thr Leu Ala Gln Thr Leu Gly Gln Asn Leu Gly	
	265 270 275 280	
30	ATG ATG TGG AAC AAA CAC CGG AGC TCG GCA GGG GAC TGC AAG TGT CCA	915
	Met Met Trp Asn Lys His Arg Ser Ser Ala Gly Asp Cys Lys Cys Pro	
	285 290 295	
35	GAC ATC TGG CTG GGC TGC ATC ATG GAG GAC ACT GGG TTC TAC CTG CCC	963
	Asp Ile Trp Leu Gly Cys Ile Met Glu Asp Thr Gly Phe Tyr Leu Pro	
	300 305 310	
40	CGC AAG TTC TCT CGC TGC AGC ATC GAC GAG TAC AAC CAG TTT CTG CAG	1011
	Arg Lys Phe Ser Arg Cys Ser Ile Asp Glu Tyr Asn Gln Phe Leu Gln	
	315 320 325	
	GAG GGT GGT GGC AGC TGC CTC TTC AAC AAG CCC CTC AAG CTC CTG GAC	1059
	Glu Gly Gly Gly Ser Cys Leu Phe Asn Lys Pro Leu Lys Leu Leu Asp	
45	330 335 340	
	CCC CCA GAG TGC GGG AAC GGC TTC GTG GAG GCA GGG GAG GAG TGC GAC	1107
	Pro Pro Glu Cys Gly Asn Gly Phe Val Glu Ala Gly Glu Glu Cys Asp	
50	345 350 355 360	
	TGC GGC TCG GTG CAG GAG TGC AGC CGC GCA GGT GGC AAC TGC TGC AAG	1155

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Cys Gly Ser Val Gln Glu Cys Ser Arg Ala Gly Gly Asn Cys Cys Lys
 365 370 375
 5 AAA TGC ACC CTG ACT CAC GAC GCC ATG TGC AGC GAC GGG CTC TGC TGT 1203
 Lys Cys Thr Leu Thr His Asp Ala Met Cys Ser Asp Gly Leu Cys Cys
 380 385 390
 10 CGC CGC TGC AAG TAC GAA CCA CGG GGT GTG TCC TGC CGA GAG GCC GTG 1251
 Arg Arg Cys Lys Tyr Glu Pro Arg Gly Val Ser Cys Arg Glu Ala Val
 395 400 405
 AAC GAG TGC GAC ATC GCG GAG ACC TGC ACC GGG GAC TCT AGC CAG TGC 1299
 15 Asn Glu Cys Asp Ile Ala Glu Thr Cys Thr Gly Asp Ser Ser Gln Cys
 410 415 420
 CCG CCT AAC CTG CAC AAG CTG GAC GGT TAC TAC TGT GAC CAT GAG CAG 1347
 Pro Pro Asn Leu His Lys Leu Asp Gly Tyr Tyr Cys Asp His Glu Gln
 20 425 430 435 440
 GGC CGC TGC TAC GGA GGT CGC TGC AAA ACC CGG GAC CGG CAG TGC CAG 1395
 Gly Arg Cys Tyr Gly Gly Arg Cys Lys Thr Arg Asp Arg Gln Cys Gln
 445 450 455
 25 GTT CTT TGG GGC CAT GCG GCT GCT GAT CGC TTC TGC TAC GAG AAG CTG 1443
 Val Leu Trp Gly His Ala Ala Ala Asp Arg Phe Cys Tyr Glu Lys Leu
 460 465 470
 30 AAT GTG GAG GGG ACG GAG CGT GGG AGC TGT GGG CGC AAG GGA TCC GGC 1491
 Asn Val Glu Gly Thr Glu Arg Gly Ser Cys Gly Arg Lys Gly Ser Gly
 475 480 485
 TGG GTC CAG TGC AGT AAG CAG GAC GTG CTG TGT GGC TTC CTC CTC TGT 1539
 35 Trp Val Gln Cys Ser Lys Gln Asp Val Leu Cys Gly Phe Leu Leu Cys
 490 495 500
 GTC AAC ATC TCT GGA GCT CCT CGG CTA GGG GAC CTG GTG GGA GAC ATC 1587
 40 Val Asn Ile Ser Gly Ala Pro Arg Leu Gly Asp Leu Val Gly Asp Ile
 505 510 515 520
 AGT AGT GTC ACC TTC TAC CAC CAG GGC AAG GAG CTG GAC TGC AGG GGA 1635
 Ser Ser Val Thr Phe Tyr His Gln Gly Lys Glu Leu Asp Cys Arg Gly
 45 525 530 535
 GGC CAC GTG CAG CTG GCG GAC GGC TCT GAC CTG AGC TAT GTG GAG GAT 1683
 Gly His Val Gln Leu Ala Asp Gly Ser Asp Leu Ser Tyr Val Glu Asp
 540 545 550
 50 GGC ACA GCC TGC GGG CCT AAC ATG TTG TGC CTG GAC CAT CGC TGC CTG 1731

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Gly Thr Ala Cys Gly Pro Asn Met Leu Cys Leu Asp His Arg Cys Leu
 555 560 565
 5 CCA GCT TCT GCC TTC AAC TTC AGC ACC TGC CCC GGC AGT GGG GAG CGC 1779
 Pro Ala Ser Ala Phe Asn Phe Ser Thr Cys Pro Gly Ser Gly Glu Arg
 570 575 580
 10 CGG ATT TGC TCC CAC CAC GGG GTC TGC AGC AAT GAA GGG AAG TGC ATC 1827
 Arg Ile Cys Ser His His Gly Val Cys Ser Asn Glu Gly Lys Cys Ile
 585 590 595 600
 15 TGT CAG CCA GAC TGG ACA GGC AAA GAC TGC AGT ATC CAT AAC CCC CTG 1875
 Cys Gln Pro Asp Trp Thr Gly Lys Asp Cys Ser Ile His Asn Pro Leu
 605 610 615
 CCC ACG TCC CCA CCC ACG GGG GAG ACG GAG AGA TAT AAA GGT CCC AGC 1923
 Pro Thr Ser Pro Pro Thr Gly Glu Thr Glu Arg Tyr Lys Gly Pro Ser
 20 620 625 630
 GGC ACC AAC ATC ATC ATT GGC TCC ATC GCT GGG GCT GTC CTG GTT GCA 1971
 Gly Thr Asn Ile Ile Ile Gly Ser Ile Ala Gly Ala Val Leu Val Ala
 635 640 645
 25 GCC TAC GTC CTG GGC GGC ACG GGC TGG GGA TTT AAA AAC ATT CGC CGA 2019
 Ala Ile Val Leu Gly Gly Thr Gly Trp Gly Phe Lys Asn Ile Arg Arg
 650 655 660
 30 GGA AGG TCC GGA GGC GCC TAAGTGCCAC CCTCCTCCCT CCAAGCCTGG 2067
 Gly Arg Ser Gly Gly Ala
 665 670
 35 CACCCACCGT CTCGGCCCTG AACCACGAGG CTGCCCCCAT CCAGCCACGG AGGGAGGCAC 2127
 CATGCAAATG TCTTCCAGGT CCAAACCCTT CAACTCCTGG CTCCGCAGGG GTTTGGGTGG 2187
 GGGCTGTGGC CCTGCCCTTG GCACCACCAG GGTGGACCAG GCCTGGAGGG CACTTCCTCC 2247
 ACAGTCCCCC ACCCACCTCC TGCGGCTCAG CCTTGACACAC CCACTGCCCC GTGTGAATGT 2307
 40 AGCTTCCACC TCATGGATTG CCACAGCTCA ACTCGGGGGC ACCTGGAGGG ATGCCCCCAG 2367
 GCAGCCACCA GTGGACCTAG CCTGGATGGC CCCTCCTTGC AACCAGGCAG CTGAGACCAG 2427
 GGTCTTATCT CTCTGGGACC TAGGGGGACG GGGCTGACAT CTACATTTTT TAAAACTGAA 2487
 TCTTAATCGA TGAATGTAAA CTCGGGGGTG CTGGGGCCAG GGCAGATGTG GGGATGTTTT 2547
 45 GACATTTACA GGAGGCCCCG GAGAACTGA GGTATGGCCA TGCCCTAGAC CCTCCCCAAG 2607
 GATGACCACA CCCGAAGTCC TGTCACCTGAG CACAGTCAGG GGCTGGGCAT CCCAGCTTGC 2667
 CCCCCTTAG CCCCCTGAG CTTGGAGGAA GTATGAGTGC TGATTCAAAC CAAAGCTGCC 2727
 TGTGCCATGC CCAAGGCCTA GGTATGGGT ACGGCAACCA CATGTCCCAG ATCGTCTCCA 2787
 50 ATTCGAAAAC AACCGTCCTG CTGTCCCTGT CAGGACACAT GGATTTTGGC AGGGCGGGGG 2847

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(B) LOCATION: 2308..3183

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Gln Gln Leu Asp Thr Arg Val Arg Gln Glu Pro Pro Gly Gly Pro Pro

EP 0 633 268 A2

	65		70		75		80	
	GTC CAT CTG GCC CAG GTG AGT TTC GTC ATC CCA GCC TTC AAC TCA AAC							288
5	Val His Leu Ala Gln Val Ser Phe Val Ile Pro Ala Phe Asn Ser Asn							
		85		90		95		
	TTC ACC CTG GAC CTG GAG CTG AAC CAC CAC CTC CTC TCC TCG CAA TAC							336
	Phe Thr Leu Asp Leu Glu Leu Asn His His Leu Leu Ser Ser Gln Tyr							
10		100		105		110		
	GTG GAG CGC CAC TTC AGC CGG GAG GGG ACA ACC CAG CAC AGC ACC GGG							384
	Val Glu Arg His Phe Ser Arg Glu Gly Thr Thr Gln His Ser Thr Gly							
		115		120		125		
15	GCT GGA GAC CAC TGC TAC TAC CAG GGG AAG CTC CGG GGG AAC CCG CAC							432
	Ala Gly Asp His Cys Tyr Tyr Gln Gly Lys Leu Arg Gly Asn Pro His							
		130		135		140		
20	TCC TTC GCC GCC CTC TCC ACC TGC CAG GGG CTG CAT GGG GTC TTC TCT							480
	Ser Phe Ala Ala Leu Ser Thr Cys Gln Gly Leu His Gly Val Phe Ser							
		145		150		155		160
25	GAT GGG AAC TTG ACT TAC ATC GTG GAG CCC CAA GAG GTG GCT GGA CCT							528
	Asp Gly Asn Leu Thr Tyr Ile Val Glu Pro Gln Glu Val Ala Gly Pro							
		165		170		175		
	TGG GGA GCC CCT CAG GGA CCC CTT CCC CAC CTC ATT TAC CGG ACC CCT							576
30	Trp Gly Ala Pro Gln Gly Pro Leu Pro His Leu Ile Tyr Arg Thr Pro							
		180		185		190		
	CTC CTC CCA GAT CCC CTC GGA TGC AGG GAA CCA GGC TGC CTG TTT GCT							624
	Leu Leu Pro Asp Pro Leu Gly Cys Arg Glu Pro Gly Cys Leu Phe Ala							
35		195		200		205		
	GTG CCT GCC CAG TCG GCT CCT CCA AAC CGG CCG AGG CTG AGA AGG AAA							672
	Val Pro Ala Gln Ser Ala Pro Pro Asn Arg Pro Arg Leu Arg Arg Lys							
40		210		215		220		
	AGG CAG GTC CGC CGG GGC CAC CCT ACA GTG CAC AGT GAA ACC AAG TAT							720
	Arg Gln Val Arg Arg Gly His Pro Thr Val His Ser Glu Thr Lys Tyr							
		225		230		235		240
45	GTG GAG CTA ATT GTG ATC AAC GAC CAC CAG CTG TTC GAG CAG ATG CGA							768
	Val Glu Leu Ile Val Ile Asn Asp His Gln Leu Phe Glu Gln Met Arg							
		245		250		255		
50	CAG TCG GTG GTC CTC ACC AGC AAC TTT GCC AAG TCC GTG GTG AAC CTG							816
	Gln Ser Val Val Leu Thr Ser Asn Phe Ala Lys Ser Val Val Asn Leu							

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EP 0 633 268 A2

	260	265	270	
	GCC GAT GTG ATA TAC AAG GAG CAG CTC AAC ACT CGC ATC GTC CTG GTT			864
5	Ala Asp Val Ile Tyr Lys Glu Gln Leu Asn Thr Arg Ile Val Leu Val			
	275	280	285	
	GCC ATG GAA ACA TGG GCA GAT GGG GAC AAG ATC CAG GTG CAG GAT GAC			912
	Ala Met Glu Thr Trp Ala Asp Gly Asp Lys Ile Gln Val Gln Asp Asp			
10	290	295	300	
	CTC CTG GAG ACC CTG GCC CGG CTC ATG GTC TAC CGA CGG GAG GGT CTG			960
	Leu Leu Glu Thr Leu Ala Arg Leu Met Val Tyr Arg Arg Glu Gly Leu			
	305	310	315	320
15	CCT GAG CCC AGT AAT GCC ACC CAC CTC TTC TCG GGC AGG ACC TTC CAG			1008
	Pro Glu Pro Ser Asn Ala Thr His Leu Phe Ser Gly Arg Thr Phe Gln			
	325	330	335	
20	AGC ACG AGC AGC GGG GCA GCC TAC GTG GGG GGC ATA TGC TCC CTG TCC			1056
	Ser Thr Ser Ser Gly Ala Ala Tyr Val Gly Gly Ile Cys Ser Leu Ser			
	340	345	350	
25	CAT GGC GGG GGT GTG AAC GAG TAC GGC AAC ATG GGG GCG ATG GCC GTG			1104
	His Gly Gly Gly Val Asn Glu Tyr Gly Asn Met Gly Ala Met Ala Val			
	355	360	365	
	ACC CTT GCC CAG ACG CTG GGA CAG AAC CTG GGC ATG ATG TGG AAC AAA			1152
30	Thr Leu Ala Gln Thr Leu Gly Gln Asn Leu Gly Met Met Trp Asn Lys			
	370	375	380	
	CAC CGG AGC TCG GCA GGG GAC TGC AAG TGT CCA GAC ATC TGG CTG GGC			1200
	His Arg Ser Ser Ala Gly Asp Cys Lys Cys Pro Asp Ile Trp Leu Gly			
35	385	390	395	400
	TGC ATC ATG GAG GAC ACT GGG TTC TAC CTG CCC CGC AAG TTC TCT CGC			1248
	Cys Ile Met Glu Asp Thr Gly Phe Tyr Leu Pro Arg Lys Phe Ser Arg			
	405	410	415	
40	TGC AGC ATC GAC GAG TAC AAC CAG TTT CTG CAG GAG GGT GGT GGC AGC			1296
	Cys Ser Ile Asp Glu Tyr Asn Gln Phe Leu Gln Glu Gly Gly Gly Ser			
	420	425	430	
45	TGC CTC TTC AAC AAG CCC CTC AAG CTC CTG GAC CCC CCA GAG TGC GGG			1344
	Cys Leu Phe Asn Lys Pro Leu Lys Leu Leu Asp Pro Pro Glu Cys Gly			
	435	440	445	
50	AAC GGC TTC GTG GAG GCA GGG GAG GAG TGC GAC TGC GGC TCG GTG CAG			1392
	Asn Gly Phe Val Glu Ala Gly Glu Glu Cys Asp Cys Gly Ser Val Gln			

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EP 0 633 268 A2

	450	455	460	
	GAG TGC AGC CGC GCA GGT GGC AAC TGC TGC AAG AAA TGC ACC CTG ACT			1440
	Glu Cys Ser Arg Ala Gly Gly Asn Cys Cys Lys Lys Cys Thr Leu Thr			
5	465	470	475	480
	CAC GAC GCC ATG TGC AGC GAC GGG CTC TGC TGT CGC CGC TGC AAG TAC			1488
	His Asp Ala Met Cys Ser Asp Gly Leu Cys Cys Arg Arg Cys Lys Tyr			
10	485	490	495	
	GAA CCA CGG GGT GTG TCC TGC CGA GAG GCC GTG AAC GAG TGC GAC ATC			1536
	Glu Pro Arg Gly Val Ser Cys Arg Glu Ala Val Asn Glu Cys Asp Ile			
	500	505	510	
15	GCG GAG ACC TGC ACC GGG GAC TCT AGC CAG TGC CCG CCT AAC CTG CAC			1584
	Ala Glu Thr Cys Thr Gly Asp Ser Ser Gln Cys Pro Pro Asn Leu His			
	515	520	525	
20	AAG CTG GAC GGT TAC TAC TGT GAC CAT GAG CAG GGC CGC TGC TAC GGA			1632
	Lys Leu Asp Gly Tyr Tyr Cys Asp His Glu Gln Gly Arg Cys Tyr Gly			
	530	535	540	
	GGT CGC TGC AAA ACC CGG GAC CGG CAG TGC CAG GTT CTT TGG GGC CAT			1680
25	Gly Arg Cys Lys Thr Arg Asp Arg Gln Cys Gln Val Leu Trp Gly His			
	545	550	555	560
	GCG GCT GCT GAT CGC TTC TGC TAC GAG AAG CTG AAT GTG GAG GGG ACG			1728
	Ala Ala Ala Asp Arg Phe Cys Tyr Glu Lys Leu Asn Val Glu Gly Thr			
30	565	570	575	
	GAG CGT GGG AGC TGT GGG CGC AAG GGA TCC GGC TGG GTC CAG TGC AGT			1776
	Glu Arg Gly Ser Cys Gly Arg Lys Gly Ser Gly Trp Val Gln Cys Ser			
35	580	585	590	
	AAG CAG GAC GTG CTG TGT GGC TTC CTC CTC TGT GTC AAC ATC TCT GGA			1824
	Lys Gln Asp Val Leu Cys Gly Phe Leu Leu Cys Val Asn Ile Ser Gly			
	595	600	605	
40	GCT CCT CGG CTA GGG GAC CTG GTG GGA GAC ATC AGT AGT GTC ACC TTC			1872
	Ala Pro Arg Leu Gly Asp Leu Val Gly Asp Ile Ser Ser Val Thr Phe			
	610	615	620	
45	TAC CAC CAG GGC AAG GAG CTG GAC TGC AGG GGA GGC CAC GTG CAG CTG			1920
	Tyr His Gln Gly Lys Glu Leu Asp Cys Arg Gly Gly His Val Gln Leu			
	625	630	635	640
	GCG GAC GGC TCT GAC CTG AGC TAT GTG GAG GAT GGC ACA GCC TGC GGG			1968
50	Ala Asp Gly Ser Asp Leu Ser Tyr Val Glu Asp Gly Thr Ala Cys Gly			

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	645	650	655	
	CCT AAC ATG TTG TGC CTG GAC CAT CGC TGC CTG CCA GCT TCT GCC TTC			2016
5	Pro Asn Met Leu Cys Leu Asp His Arg Cys Leu Pro Ala Ser Ala Phe			
	660	665	670	
	AAC TTC AGC ACC TGC CCC GGC AGT GGG GAG CGC CGG ATT TGC TCC CAC			2064
	Asn Phe Ser Thr Cys Pro Gly Ser Gly Glu Arg Arg Ile Cys Ser His			
10	675	680	685	
	CAC GGG GTC TGC AGC AAT GAA GGG AAG TGC ATC TGT CAG CCA GAC TGG			2112
	His Gly Val Cys Ser Asn Glu Gly Lys Cys Ile Cys Gln Pro Asp Trp			
	690	695	700	
15	ACA GGC AAA GAC TGC AGT ATC CAT AAC CCC CTG CCC ACG TCC CCA CCC			2160
	Thr Gly Lys Asp Cys Ser Ile His Asn Pro Leu Pro Thr Ser Pro Pro			
	705	710	715	720
20	ACG GGG GAG ACG GAG AGA TAT AAA GGT CCC AGC GGC ACC AAC ATC ATC			2208
	Thr Gly Glu Thr Glu Arg Tyr Lys Gly Pro Ser Gly Thr Asn Ile Ile			
	725	730	735	
25	ATT GGC TCC ATC GCT GGG GCT GTC CTG GTT GCA GCC ATC GTC CTG GGC			2256
	Ile Gly Ser Ile Ala Gly Ala Val Leu Val Ala Ala Ile Val Leu Gly			
	740	745	750	
	GGC ACG GGC TGG GGA TTT AAA AAC ATT CGC CGA GGA AGG TCC GGA GGC			2304
30	Gly Thr Gly Trp Gly Phe Lys Asn Ile Arg Arg Gly Arg Ser Gly Gly			
	755	760	765	
	GCC TAAGTGCCAC CCTCCTCCCT CCAAGCCTGG CACCCACCGT CTCGGCCCTG			2357
	Ala			
35	AACCACGAGG CTGCCCCCAT CCAGCCACGG AGGGAGGCAC CATGCAAATG TCTTCCAGGT			2417
	CCAAACCCTT CAACTCCTGG CTCCGCAGGG GTTTGGGTGG GGGCTGTGGC CCTGCCCTTG			2477
	GCACCACCAG GGTGGACCAG GCCTGGAGGG CACTTCCTCC ACAGTCCCCC ACCCACCTCC			2537
40	TGCGGCTCAG CCTTGACAC CCACTGCCCC GTGTGAATGT AGCTTCCACC TCATGGATTG			2597
	CCACAGCTCA ACTCGGGGGC ACCTGGAGGG ATGCCCCCAG GCAGCCACCA GTGGACCTAG			2657
	CCTGGATGGC CCCTCCTTGC AACCAGGCAG CTGAGACCAG GGTCTTATCT CTCTGGGACC			2717
	TAGGGGGACG GGGCTGACAT CTACATTTT TAAAACTGAA TCTTAATCGA TGAATGTAAA			2777
45	CTCGGGGGTG CTGGGGCCAG GGCAGATGTG GGGATGTTTT GACATTTACA GGAGGCCCCG			2837
	GAGAACTGA GGTATGGCCA TGCCCTAGAC CCTCCCCAAG GATGACCACA CCCGAAGTCC			2897
	TGTCACCTGAG CACAGTCAGG GGCTGGGCAT CCCAGCTTGC CCCCCTTAG CCCCCTGAG			2957
50	CTTGAGGAA GTATGAGTGC TGATTCAAAC CAAAGCTGCC TGTGCCATGC CCAAGGCCTA			3017
	GGTTATGGGT ACGGCAACCA CATGTCCCAG ATCGTCTCCA ATTCGAAAAC AACCGTCTCTG			3077

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CTGTCCCTGT CAGGACACAT GGATTTTGGC AGGGCGGGGG GGGGTTCTAG AAAATATAGG 3137
TTCCTATAAT AAAATGGCAC CTTCCCCCTT TAAAAAAAAA AAAAAA 3183

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(2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS:

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- (A) LENGTH: 9278 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDNESS: double
- (D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: Genomic DNA

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Homo sapiens

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(vii) IMMEDIATE SOURCE:

- (A) LIBRARY: human DNA cosmid library

(ix) FEATURE:

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- (A) NAME/KEY: exon 1
- (B) LOCATION: 28..44

(ix) FEATURE:

- (A) NAME/KEY: exon 2
- (B) LOCATION: 308..374

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(ix) FEATURE:

- (A) NAME/KEY: exon 3
- (B) LOCATION: 909..994

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(ix) FEATURE:

- (A) NAME/KEY: exon 4
- (B) LOCATION: 1081..1156

(ix) FEATURE:

40

- (A) NAME/KEY: exon 5
- (B) LOCATION: 1591..1657

(ix) FEATURE:

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- (A) NAME/KEY: exon 6
- (B) LOCATION: 1725..1792

(ix) FEATURE:

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- (A) NAME/KEY: exon 7
- (B) LOCATION: 2182..2256

(ix) FEATURE:

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EP 0 633 268 A2

5 (A) NAME/KEY: xon 8
(B) LOCATION: 2339..2410
(ix) FEATURE:
(A) NAME/KEY: exon 9
(B) LOCATION: 2588..2754
10 (ix) FEATURE:
(A) NAME/KEY: exon 10
(B) LOCATION: 3248..3332
(ix) FEATURE:
15 (A) NAME/KEY: exon 11
(B) LOCATION: 3445..3535
(ix) FEATURE:
(A) NAME/KEY: exon 12
20 (B) LOCATION: 3645..3696
(ix) FEATURE:
(A) NAME/KEY: exon 13
25 (B) LOCATION: 4014..4113
(ix) FEATURE:
(A) NAME/KEY: exon 14
(B) LOCATION: 4196..4267
30 (ix) FEATURE:
(A) NAME/KEY: exon 15
(B) LOCATION: 4386..4478
(ix) FEATURE:
35 (A) NAME/KEY: exon 16
(B) LOCATION: 4920..5000
(ix) FEATURE:
40 (A) NAME/KEY: exon 17
(B) LOCATION: 5347..5397
(ix) FEATURE:
(A) NAME/KEY: exon 18
45 (B) LOCATION: 5501..5564
(ix) FEATURE:
(A) NAME/KEY: exon 19
50 (B) LOCATION: 5767..5866
(ix) FEATURE:

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(A) NAME/KEY: exon 20
 (B) LOCATION: 6073..6202

5 (ix) FEATURE:
 (A) NAME/KEY: exon 21
 (B) LOCATION: 6300..6468

10 (ix) FEATURE:
 (A) NAME/KEY: exon 22
 (B) LOCATION: 6557..6671

15 (ix) FEATURE:
 (A) NAME/KEY: exon 23
 (B) LOCATION: 6756..6846

20 (ix) FEATURE:
 (A) NAME/KEY: exon 24
 (B) LOCATION: 7829..7846

25 (ix) FEATURE:
 (A) NAME/KEY: exon 25
 (B) LOCATION: 8165..9038

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9

GC GTT TACTG GCAAACCGCA TTTGTAA ATG TGC TGG CTG AGC CA NNNNNNNNNN 54
 Met Cys Trp Leu Ser His
 1 5

NNNNCCAGGT GAGTTTCGTC ATCCAGCCTT CAACTCAAAC TTCACCCTGG ACCTGGAGCT 114
 GAACCAAGTGA GNGTGGCCTT GAGCCCAAGA GGAAGGGCAG TGGTGGNNNG GGGGAGACAT 174
 35 GGCTAGGGCC TGGCTGCTGG GGGTCTGGGG GTTGGGCCTG GCGAGAGGGG ACCTGGGTCC 234
 TGACCTGAGG CGAGCCTAAA GCCCGACCTC ACCTCGCCCG TGACCCCCCT TCCTGCTGCC 294
 CCCTCTGTCT CAG C CAA CTC CTC TCC TCG CAA TAC GTG GAG CGC CAC TTC 344
 40 Gln Leu Leu Ser Ser Gln Tyr Val Glu Arg His Phe
 10 15

AGC CGG GAG GGG ACA ACC CAG CAC AGC ACC GTGAGTGCCA CTGCTGGGGA 394
 Ser Arg Glu Gly Thr Thr Gln His Ser Thr
 20 25

CCGGGGCCCG GGATGGAAGG GAGGTGCTGT TTCTGTGGTT CTGTGGTCAC AGGTGTAGGG 454
 ACAGGTGGCC ACTGGAGATG GGGTCCTGGG CCTGGCCCTC CAGCACCTTC CCTCTCTCCC 514
 50 GACCCAGGAG GCTCTGAGGG TGGACAGTGG GCAGCTTAGT GCATAGGGCC CTGAAGTCCC 574
 CTCACCTGGC CCCAGAGCTC TGACCCCCAG CCAGCCCACG TGGGGCCTAC AGGGACACTC 634

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GTTCCGAGCA GGCTGCCAGG ATCCNNNNNN NNNNNNATAG ATGACGTGAA GGAGGCCAG 694
 AGGTTCTTAA CCCCAGAGGG CTAGGAACCTT GCCCAGGGTG GCACGGCAAA TTAGGAGCAC 754
 5 CAGCCATCTA GAAACAGGCT CCAGAGCCCC AGGNATACCC AGGGATNGTG GCCACCTGCA 814
 CACAGGGCAG CTTCAGTGTC CCCCAGGAGC CATTGGCTGC CCCCAGGCTC 874
 ATGCCAGCGT TCTGCTCACT GTTCTGCTCC TTAG GGG GCT GGA GAC CAC TGC TAC 929
 Gly Ala Gly Asp His Cys Tyr
 10 30 35
 TAC CAG GGG AAG CTC CGG GGG AAC CCG CAC TCC TTC GCC GCC CTC TCC 977
 Tyr Gln Gly Lys Leu Arg Gly Asn Pro His Ser Phe Ala Ala Leu Ser
 15 40 45 50
 ACC TGC CAG GGG CTG CA GTGAGTATGG GGAGGGGCCG GGCAGCTGGG 1024
 Thr Cys Gln Gly Leu His
 55
 20 AGAAGCCTCT GGCCAGGCC TGGGGACGGA GGGGAGCTGC GCCTCTCTCT CCACAG T 1081
 GGG GTC TTC TCT GAT GGG AAC TTG ACT TAC ATC GTG GAG CCC CAA GAG 1129
 Gly Val Phe Ser Asp Gly Asn Leu Thr Tyr Ile Val Glu Pro Gln Glu
 60 65 70
 25 GTG GCT GGA CCT TGG GGA GCC CCT CAG GTAAGCCCCA CACAACCCCT 1176
 Val Ala Gly Pro Trp Gly Ala Pro Gln
 75 80
 30 TGCCATCCTC TCTGGTGGCC CTGCCAAGCT TGTCCCAACA GCTGTTGCTG CCACCTCTTC 1236
 CTCCTCCGGC TCCTCCCTCA GTAACCCAG CCTCACTGCC CTCTTCAGTG ACCCCAGCTC 1396
 TGGTTCCCTC CCTCCTGTGC CCCAGCTCCC CCTGTGCCCC CAGCTCCAAT GTCCATCTG 1356
 TCCCATAGT GACCTCCCAT TGGGCTCCAA TGTCTTTG CCGTGTCTCT CAGGGTGCCC 1416
 35 CCAGGTCTTG ACCCCGGAAT CTGAGCATCT GGGAGATCAG ATCCGACATG GGAGCTGTGG 1476
 CCAGTTCTGG GTCACCCAG GGTGGGGTGG AGGCGAGGGC TGGATCTGGC CCCCAGCAAG 1536
 TGGCCTGGAG CAGGCCAGT TGGCACCCA AGAACTAATT TCCCCTCATT GCAG GGA 1593
 Gly
 40 CCC CTT CCC CAC CTC ATT TAC CGG ACC CCT CTC CTC CCA GAT CCC CTC 1641
 Pro Leu Pro His Leu Ile Tyr Arg Thr Pro Leu Leu Pro Asp Pro Leu
 85 90 95
 45 GGA TGC AGG GAA CCA G GTAAGGGAGG GGAGGGGGG TGGGGAGGGG CCNGGCTGTG 1697
 Gly Cys Arg Glu Pro Gly
 100
 CCCCCCTCAC CTGCCCCTCC CCGACAG GC TGC CTG TTT GCT GTG CCT GCC CAG 1750
 50 Cys Leu Phe Ala Val Pro Ala Gln

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105 110
 TCG GCT CCT CCA AAC CGG CCG AGG CTG AGA AGG AAA AGG CAG 1792
 Ser Ala Pro Pro Asn Arg Pro Arg Leu Arg Arg Lys Arg Gln
 115 120 125
 GTACGGGGGC CCGCACAGAC CTCGGGCTGC AGAGACCTCG GGCTGCAGAG AGACCTCGGC 1852
 CGTGGCCCCAG AGCAGGAGGG CACCCTCATC TATGGCTGGG GCGAAGGAAG GCTCAGATGG 1912
 10 ATGTGGCTGG GGGCCAGGGA CCGTGTCTGG GAGAAGCCCC CACCCTTCC CTAATGCTGG 1972
 CATCTACAGA GGCCCCATCC TGGGCAAACC GAGGCTGCCT GCCCTCATTC CAAAGCTGAG 2032
 GAAGGACAGG ACCCTCTGCC AGTGGGGAGC TGGCACTGTC CCTGGCTGGA GTCCAGACCC 2092
 15 CCCCATCCCC ACCGAGTCTG TTCCTGGCTT GGCCATGAGA TCAGTCAGAC ATGGAAGGGA 2152
 CTGATTCCAA GTGCCACCC ACCCCCCAG GTC CGC CGG GGC CAC CCT ACA GTG 2205
 Val Arg Arg Gly His Pro Thr Val
 130 135
 20 CAC AGT GAA ACC AAG TAT GTG GAG CTA ATT GTG ATC AAC GAC CAC CAG 2253
 His Ser Glu Thr Lys Tyr Val Glu Leu Ile Val Ile Asn Asp His Gln
 140 145 150
 CTG GTGAGTGCCA GGGCAGGGAC AGGGCGTGAC ACTGGGAGGC CCCTGAGGAG 2306
 25 Leu
 CCTGGCCCTC CTCCCATTCT TCTCTCTCCC AG TTC GAG CAG ATG CGA CAG TCG 2359
 Phe Glu Gln Met Arg Gln Ser
 155
 30 GTG GTC CTC ACC AGC AAC TTT GCC AAG TCC GTG GTG AAC CTG GCC GAT 2407
 Val Val Leu Thr Ser Asn Phe Ala Lys Ser Val Val Asn Leu Ala Asp
 160 165 170 175
 35 GTG GTAAGCAGCT CTCCCTCCCT CCCTTCCCTC CTCCTCATGC CCCCCACCC 2460
 Val
 CACCACACAC ATTAGGGGGC ACTGTCAGCC CCTGGCTCCC ACTTCCTGGA GAGAACAGAC 2520
 40 AGGCCCTCCT CCAGCCCTGG CCCCACACC CACTCCCACC CTCCAGCCCC CCTCATCTTC 2580
 TCCCCAG ATA TAC AAG GAG CAG CTC AAC ACT CGC ATC GTC CTG GTT GCC 2629
 Ile Tyr Lys Glu Gln Leu Asn Thr Arg Ile Val Leu Val Ala
 180 185 190
 45 ATG GAA ACA TGG GCA GAT GGG GAC AAG ATC CAG GTG CAG GAT GAC CTC 2677
 Met Glu Thr Trp Ala Asp Gly Asp Lys Ile Gln Val Gln Asp Asp Leu
 195 200 205
 CTG GAG ACC CTG GCC CGG CTC ATG GTC TAC CGA CGG GAG GGT CTG CCT 2725
 50 Leu Glu Thr Leu Ala Arg Leu Met Val Tyr Arg Arg Glu Gly Leu Pro

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210 215 220
 5 GAG CCC AGT AAT GCC ACC CAC CTC TTC TC GTGAGTCCCC CACCCTGCAC 2774
 Glu Pro Ser Asn Ala Thr His Leu Phe Ser
 225 230
 10 CTCCTGCCAG CCTCTGCTAG TTGCTACAGT GCTTGGGATT ACTTAACACC TGCCCTGTGC 2834
 TGGCTGCTCC TCTCAGAGTC TGGGGACTGG GCTCACCTTG CACCTGCCAC CTACCCCCAG 2894
 CCACATGCAA CAGCTGGGCA TCATCCCCTG AATCTGAGGT TGATGCCCTT GTCTTAGCCC 2954
 TGGTGGTCCT CTTCTGCCTC TCACCTCCCC TTAGTTCTGT CTTCCCTTC AACTGTCCCN 3014
 NNNNNNNNNN NAGAGTGAAG CTCTGTCTCA AAAGAAAAAN AAAANAAAAG AAGAAAAAAA 3074
 15 AGAACCCAAG GAGCGGGGA AGGGTCTTGC CTGGGGTCAC CAAGGCTGAT GTAAAGGGCC 3134
 AGGCTCACCT CCTGAGGAAG GACTCTAGTG TGAGGGGCTC CCAAGGCC CACCACCACC 3194
 CGGGGAGCCA CAGGGGAGGG CAGAAGCCAT CCTGACAGCG CACTCCCTTC CAG G GGC 3251
 Gly
 20 AGG ACC TTC CAG AGC ACG AGC AGC GGG GCA GCC TAC GTG GGG GGC ATA 3299
 Arg Thr Phe Gln Ser Thr Ser Ser Gly Ala Ala Tyr Val Gly Gly Ile
 235 240 245
 25 TGC TCC CTG TCC CAT GGC GGG GGT GTG AAC GAG GTGAGCAGTG 3342
 Cys Ser Leu Ser His Gly Gly Gly Val Asn Glu
 250 255 260
 30 GGGGGACATG GCTGGGGTGG CGGCTGAGGG AAAGGGGCTT AGGGGCACGA CGTGCCTGNT 3402
 TGGAAGATGT AGACATCTGT GCCCCATCTT CCCCACCCCC AG TAC GGC AAC ATG 3456
 Tyr Gly Asn Met
 GGG GCG ATG GCC GTG ACC CTT GCC CAG ACG CTG GGA CAG AAC CTG GGC 3504
 35 Gly Ala Met Ala Val Thr Leu Ala Gln Thr Leu Gly Gln Asn Leu Gly
 265 270 275 280
 ATG ATG TGG AAC AAA CAC CGG AGC TCG GCA G GTATCCTCCC CCAGAGGCCC 3555
 Met Met Trp Asn Lys His Arg Ser Ser Ala Gly
 40 285 290
 CCGTGTGGCC CAGCAGCTCT GGAACGGGAG GGTGACAGTG GGAGGGGTGG TCCTTGGCCT 3615
 CCCTCATATC CGCCTGGCTC ACCCCTCAG GG GAC TGC AAG TGT CCA GAC ATC 3667
 Asp Cys Lys Cys Pro Asp Ile
 45 295
 TGG CTG GGC TGC ATC ATG GAG GAC ACT GG GTGAGTTCTT GGGGACAACC 3716
 Trp Leu Gly Cys Ile Met Glu Asp Thr Gly
 50 300 305
 GGGGGAAGGT CTTGGGCGAG GGGAGTCTTA GAGCGAGCAT TGTTTGGCAG TCTGGACCAG 3776

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GGGNNNNNNN NNNNNGAACA CACCTTCCCT TCCAGGCCGG CTTGCGAGTC CCAGGTTCAA 3836
 GCGAGGGATG GGAGCGACAA GGGACAAGGC GGAGGATTCT GGTGCAATCC CGGGGCAGAT 3896
 5 CCTCCGCCTC CTCGCGATGG TGACGAAGTC CCCAGTGTA CCCCCTCCCC AGCCTTGAGA 3956
 GGGGTGAGGG TGGGTTGGAG GGGAGCAGCC AGCAGCACCT CCCCTCGCCC TATCCAG G 4014
 TTC TAC CTG CCC CGC AAG TTC TCT CGC TGC AGC ATC GAC GAG TAC AAC 4062
 Phe Tyr Leu Pro Arg Lys Phe Ser Arg Cys Ser Ile Asp Glu Tyr Asn
 10 310 315 320
 CAG TTT CTG CAG GAG GGT GGT GGC AGC TGC CTC TTC AAC AAG CCC CTC 4110
 Gln Phe Leu Gln Glu Gly Gly Gly Ser Cys Leu Phe Asn Lys Pro Leu
 15 325 330 335 340
 AAG GTACCAGCCC CGCGCGGGG AGCATGGGAG CGGGCCCTGG GCGGGGTCCG 4163
 Lys
 GGCCAGACTC CCGACCTGTC CTCCCCCTCC AG CTC CTG GAC CCC CCA GAG TGC 4216
 20 Leu Leu Asp Pro Pro Glu Cys
 345
 GGG AAC GGC TTC GTG GAG GCA GGG GAG GAG TGC GAC TGC GGC TCG GTG 4264
 Gly Asn Gly Phe Val Glu Ala Gly Glu Glu Cys Asp Cys Gly Ser Val
 25 350 355 360
 CAG GTGAGCGGTG GTGCGGGCGC CAGGTGGGGA ACCGGGATGC GGGGGTGGGC 4317
 Gln
 30 365
 ACCAGGGAGC GTCTGAGTGG GAGGATTAGG GCTCGCCCGC CTCCTTCCCC TCCTCCCGCG 4377
 TCCCTCAG GAG TGC AGC CGC GCA GGT GGC AAC TGC TGC AAG AAA TGC ACC 4427
 Glu Cys Ser Arg Ala Gly Gly Asn Cys Cys Lys Lys Cys Thr
 35 370 375
 CTG ACT CAC GAC GCC ATG TGC AGC GAC GGG CTC TGC TGT CGC CGC TGC 4475
 Leu Thr His Asp Ala Met Cys Ser Asp Gly Leu Cys Cys Arg Arg Cys
 40 380 385 390 395
 AAG GTAAGCAGGA CCGGCCGGGA GGCGGGGCCA GGACGCAGGA GGAGCGATTG 4528
 Lys
 GAGGCCTTCA TATAAGGGGT GGGAGCTAGG GAGGGAAGCG GAGCCTTCGG GGACGAAGGC 4588
 45 CTCTGGGGCA GGGCTTGATG CGAAGACAGC GCCAATGGGA GCAAGGGCGG GCTGAAGGAT 4648
 GTTGAAGGCN NNNNNNNNNN NNNCGGACGG GAAGCTCCCA GAATCAAGGA GGGCGGGAAG 4708
 GTGGGCGGGC TTGGGGCGGT GCTGAGTGC GCTGGGAGCGA GGTGGGGAGC GTTCAAGAGG 4768
 TGGTGGGAGC AGGGAAATAA GAACAGGCCT AAACGGGGCC CTGGGGAGCT GGAGGGCCCCG 4828
 50 GGGATGTGGG GGTCCAGAGA GCGGGGGGCC TGGGGAGGGC AGGGCCGAGG CATCCATCCT 4888

55

GCCTGACTCG AGGAGCGCGT CTCTTCCCTA G TAC GAA CCA CGG GGT GTG TCC 4940
 Tyr Glu Pro Arg Gly Val Ser
 400

5 TGC CGA GAG GCC GTG AAC GAG TGC GAC ATC GCG GAG ACC TGC ACC GGG 4988
 Cys Arg Glu Ala Val Asn Glu Cys Asp Ile Ala Glu Thr Cys Thr Gly
 405 410 415

10 GAC TCT AGC CAG GTCCGCCCGG CCCC GCCGTC TTGTGGAGCC CTGGGCGAGG 5040
 Asp Ser Ser Gln
 420

15 CAACCCCTAC CCTTGTCGAT TTGGTTTTCC CGGACGAGTG CTCAGCACTC CCCTCCTCTC 5100
 CACAGCTGGC ATCGACCTTC ACTGATCAGA CTGTTTTCTT ATCTGAGAAA GGGGTTCCTC 5160
 ATGCTCCTGG CCTTGTTCTT TCAATCATT AACCAGAATG TATCGTCTGG CTGGTATCCC 5220
 AGCGCCTGGG CCCGGTGNNN NNNNNNNNTA CCCAGATTCC TCCTGGGCAG CCCTCAGCTC 5280

20 CAGTCTGGG CAGCCCTCAG CCCAGTCTG GGA CTGCTCC GCTCAACCCC ACCCTCTCT 5340
 CCACAG TGC CCG CCT AAC CTG CAC AAG CTG GAC GGT TAC TAC TGT GAC 5388
 Cys Pro Pro Asn Leu His Lys Leu Asp Gly Tyr Tyr Cys Asp
 425 430 435

25 CAT GAG CAG GTATGATGGC TGCCCCCTGA GCCTGGGATT CAGGGCAGTC 5437
 His Glu Gln
 440

30 TCTTATCTCC ACTCTGACCA CTCAGCATCT CCATCCCTTG CCTCTTAATT CTGGACTCT 5497
 CAG GGC CGC TGC TAC GGA GGT CGC TGC AAA ACC CGG GAC CGG CAG TGC 5545
 Gly Arg Cys Tyr Gly Gly Arg Cys Lys Thr Arg Asp Arg Gln Cys
 445 450 455

35 CAG GTT CTT TGG GGC CAT G GTGAGTCTGC TAGGGCTGGA GTGGGACTCC 5594
 Gln Val Leu Trp Gly His Ala
 460

40 GGAGGAGCCC AGAGCTGAGA AGCTGGGGAG AGTGGGTTCC AGCTGAACAG GCCCCCAAGT 5654
 GTGTAGCTCC CCAGGATCTC AGGGAGCCCA GGCAGAGTGT GGGAGATGCA GGCCTGAGGT 5714
 CTTGGGGTGG GTCCTGGGGC ACGTGGGGTC ACTTGGCATC CTCTCCCCAC AG CG GCT 5771
 Ala

45 GCT GAT CGC TTC TGC TAC GAG AAG CTG AAT GTG GAG GGG ACG GAG CGT 5819
 Ala Asp Arg Phe Cys Tyr Glu Lys Leu Asn Val Glu Gly Thr Glu Arg
 465 470 475

50 GGG AGC TGT GGG CGC AAG GGA TCC GGC TGG GTC CAG TGC AGT AAG CA 5866
 Gly Ser Cys Gly Arg Lys Gly Ser Gly Trp Val Gln Cys Ser Lys Gln

55

480 485 490 495
 GTGAGTACTG AGGCTCCAG AGGGCCTCTC AGCTCCAGGG CAGGTGTGAG ACTTTTCAGA 5926
 5 GATGGGGTAG TAGGTTCTCC CAGGAGGAGC CTGTCAAGTCC CAATGGGCGG GCACGTGGCA 5986
 AATGAGGTGG CAGGGTGCAG GGTGAGGGCA GATTAGAGTT CAGTAGTTGA GTCTGAGGTC 6046
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 Pro Gln Gln Gly Arg Ala Val Trp
 10 500
 CTT CCT CCT CTG TGT CAA CAT CTC TGG AGC TCC TCG GCT AGG GGA CCT 6145
 Leu Pro Pro Leu Cys Gln His Leu Trp Ser Ser Ser Ala Arg Gly Pro
 15 505 510 515
 GGT GGG AGA CAT CAG TAGTGTCAAC TTCTACCACC AGGGCAAGGA GCTGGACTGC 6200
 Gly Gly Arg His Gln
 20 520
 AGGTGCTGAC CAGCACCAAA ACTCAGGGAG GGGACCTGGC AGCTGTGCTG GGGGTTAGAA 6260
 GATCTGGGGG CTGGAGGCTG GGCTGTGTCA CTTCCCCAGG GGAGGCCACG TGCAGCTGGC 6320
 GGACGGCTCT GACCTGAGCT ATGTGGAGGA TGGCACAGCC TGCGGGCCTA ACATGTTGTG 6380
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 GGAGCGCCGG ATTTGCTCCC ACCACGGGGT GACTGCCTGG AGCCCGGGAT GCGGGGAGAA 6500
 GCTTACAAGA GGGGACAGGC CCCTGCTCAC CTCTCCTGGC CCTGCCCCTG CTCTAGGTCT 6560
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 30 ATAACCCCTT GCCCACGTCC CCACCCACGG GGGAGACGGA GAGATATAAA GGTGAGGCTG 6680
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 CTGCCATCCT CCCAGGTCCC AGCGGCACCA ACATCATCAT TGGCTCCATC GCTGGGGCTG 6800
 TCCTGGTTGC AGCCATCGTC CTGGGCGGCA CGGGCTGGGG ATTTAAGTAA GAGACACACA 6860
 35 CACCCTGTGC CCCCTGGCAT CCTTGAGGGG GGATCAGAAT CCCTACTGGT GGAGCTGAGG 6920
 GGGCCCTCCC TGAAAGCCCA ACTGAACCAG AGCTCACACG TCATAGGTCC AAGTAGCCTG 6980
 CAGGGCTTAA CATTTAGAAA CTAGGAGATT TTAGGCTAGA TGAGGTGCTC ACGCCTGTAA 7040
 40 TCCCAGCACT TTGGGAGGCC AAGGCAGGCG GATCACCTGA GGTCAGGAAT TCAAGACCAG 7100
 TCTGGCCAAC ATGGTGAAAC CCGTCTCTAT TAAAAATACA AAAATTAGCC AGCCATGGTG 7160
 GTGCACACCT GTAATCCCAG CTACTTGCAG GGCTGAGGCA GAGAATTGCT TGAACCCGGG 7220
 AGGTGGAGGT TGCAGTGAGC TGAGATCGCA CCATTGCACT CCAGCCTTGG GTGACAGAGC 7280
 45 AAGACTGCGT CAAAAA AAAA AAAAAGGA AAGAAAGAGA GAAAGAAAAG 7340
 AAAAGAGAAA AGAAATCAGG AGATTTTACA CTAGCAATTC GGATTTCCAG CTCTGGAAAC 7400
 ATGAAAAGGT TGAGCCCCAG CGTGCCCTTA AGCATCCCCA AATAGCCACA GAGTGGAGCT 7460
 50 GGGCAGGGGC CACCCAAGCC AGGCATGTGT CCTCCAGTCT CCAGTTCCCA CCAGCCTATA 7520
 CTCCTTTGTG CGTGTCTAAG TTTGGGGTCC TTGTGCCTGG TCTTACCCCC CTTAATGTGC 7580

55

AGAGGGAGGA ACCCACGGCC CAAGGTCACA TGATTGAGTT AGTAGCAGAG TCAGAGCTGG 7640
 AACCGGGACG CATTTTTGTG GGTGCCCTGG GTAATTCTCC CTGGCCCTTA CATTAGTGTC 7700
 5 CAGGCCCCCG GGACCCCGGC CCCGCTCTGG GGCAAGGGGT CGCATGGCAG CCAAAGGCCC 7760
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 CCCTGCAGAA ACATTGCGCG AGGAAGGTAC GACCCGACCC AGCTGGGGGC AGTGTGATGC 7880
 10 CGGCCACGTC ATCCCTCCCG CTGTCCTTGT CTCCTCCATC TCATTGTCGA CCCGCGTTCT 7940
 GTTGATGGGG TCGGGGGCCG ATCCCACCCT GCGTGCCNNN NNNNNNNNNN ATCTGTTTTG 8000
 TCTTCCATAT CACCACTGTC TGACCTCCCG CAGATCCCTT CCCTGGCCAG CCTGTGACTT 8060
 GCCGCTGCC TCCAGGGCCC AGAACTGAGC TCCGGGGCCC TGCTGGGGGG CTCTCCCCGA 8120
 15 GGCCCTGCT CACGTCCTCC CCTGATGCCC CCTCTCCGTT CCAGGTCCGG AGGGGCCTAA 8180
 GTGCCACCCT CCTCCCTCCA AGCCTGGCAC CCACCGTCTC GGCCCTGAAC CACGAGGCTG 8240
 CCCCCATCCA GCCACGGAGG GAGGCACCAT GCAAATGTCT TCCAGGTCCA AACCTTCAA 8300
 CTCCTGGCTC CGCAGGGGTT TGGGTGGGGG CTGTGGCCCT GCCCTTGGCA CCACCAGGGT 8360
 20 GGACCAGGCC TGGAGGGCAC TTCCTCCACA GTCCCCCACC CACCTCCTGC GGCTCAGCCT 8420
 TGCACACCCA CTGCCCCGTG TGAATGTAGC TTCCACCTCA TGGATTGCCA CAGCTCAACT 8480
 CGGGGACACC TGGAGGGATG CCCCCAGGCA GCCACCAGTG GACCTAGCCT GGATGGCCCC 8540
 25 TCCTTGCAAC CAGGCAGCTG AGACCAGGGT CTTATCTCTC TGGGACCTAG GGGGACGGGG 8600
 CTGACATCTA CATTTTTTAA AACTGAATCT TAATCGATGA ATGTAAACTC GGGGGTGCTG 8660
 GGGCCAGGGC AGATGTGGGG ATGTTTTGAC ATTTACAGGA GGCCCCGGAG AAAGTGAGGT 8720
 ATGGCCATGC CCTAGACCCT CCCCAGGAT GACCACACCC GAAGTCCTGT CACTGAGCAC 8780
 30 AGTCAGGGGC TGGGCATCCC AGCTTGCCCC CGCTTAGCCC CGCTGAGCTT GGAGGAAGTA 8840
 TGAGTGCTGA TTCAAACCAA AGCTGCCTGT GCCATGCCCA AGGCCTAGGT TATGGGTACG 8900
 GCAACCACAT GTCCAGATC GTCTCCAAT CGAAAACAAC CGTCCTGCTG TCCCTGTCAG 8960
 GACACATGGA TTTTGGCAGG GCGGGGGGGG GTTCTAGAAA ATATAGGTTC CTATAATAAA 9020
 35 ATGGCACCTT CCCCCTTTNN NNNNNNNNNN NNNGGGATAC CTCTGAATAT GGGTATCTGG 9080
 GGCTGGATAT GGGTGGGACA TGAGACTTCC TGTGACCAGC CACCCTGGCT CCCAGCTCTC 9140
 TGTATCCTCC TGCCCCGCCC TGGGGGGTGC CTACCCTGGN AGAACCCAGG GAGGAGTGGA 9200
 40 GGCTGCCTCT GCCTGGGCCT CCACACAGCA TCCTGACATA CGCCACCTGG GGTGGGGGTG 9260
 GGGAGGCAGG GCCAGGAG 9278

45

(2) INFORMATION FOR SEQ ID NO: 10:

50

(i) SEQUENCE CHARACTERISTICS:

55

- 5 (A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

10 (ii) MOLECULE TYPE: DNA (genomic)

15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

GCACCTGCCC CGGCAGT

17

20 (2) INFORMATION FOR SEQ ID NO: 11:

- (i) SEQUENCE CHARACTERISTICS:
25 (A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

30 (ii) MOLECULE TYPE: DNA (genomic)

35 (iii) ANTI-SENSE: YES

40 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

CCAGGACAGC CCCAGCGATG

20

45 (2) INFORMATION FOR SEQ ID NO: 12:

- (i) SEQUENCE CHARACTERISTICS:
50 (A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid

55

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

5

(ii) MOLECULE TYPE: DNA (genomic)

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

15

GGCTGCTGAT CGCTTCTGCT AC

22

(2) INFORMATION FOR SEQ ID NO: 13:

20

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

25

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

30

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

35

GAGAAGCTGA ATGTGGAGGG

20

(2) INFORMATION FOR SEQ ID NO: 14:

40

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19 base pairs

(B) TYPE: nucleic acid

45

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

50

(ii) MOLECULE TYPE: DNA (genomic)

55

(iii) ANTI-SENSE: YES

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

10

GTCAGAGCCG TCCGCCAGC

19

(2) INFORMATION FOR SEQ ID NO: 15:

15

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22 base pairs

(B) TYPE: nucleic acid

20

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

25

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

30

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

35

GCCATCCTCC ACATAGCTCA GG

22

(2) INFORMATION FOR SEQ ID NO: 16:

40

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 26 base pairs

(B) TYPE: nucleic acid

45

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

50

(ii) MOLECULE TYPE: DNA (genomic)

55

(iii) ANTI-SENSE: YES

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

10

GATGTAAGTC AAGTTCCCAT CAGAGA

26

(2) INFORMATION FOR SEQ ID NO: 17:

15

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 25 base pairs

(B) TYPE: nucleic acid

20

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

25

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

30

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

35

AACAGCTGGT GGTCGTTGAT CACAA

25

(2) INFORMATION FOR SEQ ID NO: 18:

40

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs

(B) TYPE: nucleic acid

45

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

50

(ii) MOLECULE TYPE: DNA (genomic)

55

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

5 ATGAGGCTGC TCGGCGCTG

20

(2) INFORMATION FOR SEQ ID NO: 19:

10

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 27 base pairs

(B) TYPE: nucleic acid

15

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

20

25

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

CACAGATCTG GGGGCATATG CTCCTG

27

30

(2) INFORMATION FOR SEQ ID NO: 20:

(i) SEQUENCE CHARACTERISTICS:

35

(A) LENGTH: 27 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

40

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

45

(iii) ANTI-SENSE: YES

50

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20:

55 AACAAAGCTTC TACTGATGTC TCCCACC

27

Claims

1. An MDC protein which comprises the whole or part of the protein represented by SEQ ID NO:1, or which consists of a protein substantially equivalent to one comprising the whole or part of the protein represented by SEQ ID NO:1.
2. The MDC protein as claimed in claim 1, which comprises the whole or part of the protein represented by SEQ ID NO:2, or which consists of a protein substantially equivalent to one comprising the whole or part of the protein represented by SEQ ID NO:2.
3. The MDC protein as claimed in claim 1, which comprises the whole or part of the protein represented by SEQ ID NO:3, or which consists of a protein substantially equivalent to one comprising the whole or part of the protein represented by SEQ ID NO:3.
4. The MDC protein as claimed in claim 1, which comprises the whole or part of the protein represented by SEQ ID NO:4, or which consists of a protein substantially equivalent to one comprising the whole or part of the protein represented by SEQ ID NO:4.
5. The MDC protein as claimed in any of the claims 1 to 4, comprising a polypeptide having an amino acid sequence consisting of continuous at least 3 to 5 amino acids, at least 8 to 10 amino acids, at least 11 to 20 amino acids, or more than 20 amino acids in the sequence represented by the SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3 or SEQ ID NO:4.
6. The MDC protein as claimed in any of the claims 1 to 5 comprising a protein substantially equivalent to one comprising the whole or part of the protein represented by SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, or SEQ ID NO:4, wherein one or more amino acids have been replaced, deleted and/or inserted, but still producing an equal effect in research and diagnosing.
7. The MDC protein as claimed in claim 1, which comprises a polypeptide having an amino acid sequence consisting of continuous, at least eight amino acids in the sequence represented by the SEQ ID NO:1.
8. A DNA encoding the MDC protein as claimed in claim 1, which comprises the whole or part of the DNA represented by SEQ ID NO:5, or which consists of a DNA substantially equivalent to one comprising the whole or part of the DNA represented by SEQ ID NO:5.
9. The DNA as claimed in claim 8, which comprises the whole or part of the DNA represented by SEQ ID NO:6, or which consists of a DNA substantially equivalent to one comprising the whole or part of the DNA represented by SEQ ID NO:6.
10. The DNA as claimed in claim 8, which comprises the whole or part of the DNA represented by SEQ ID NO:7, or which consists of a DNA substantially equivalent to one comprising the whole or part of the DNA represented by SEQ ID NO:7.
11. The DNA as claimed in claim 8, which comprises the whole or part of the DNA represented by SEQ ID NO:8, or which consists of a DNA substantially equivalent to one comprising the whole or part of the DNA represented by SEQ ID NO:8.
12. The DNA as claimed in any of the claims 8 to 11, comprising a DNA sequence consisting of at least 6 bases, at least 8 bases, at least 10 to 12 bases or about 15 to 25 bases.
13. A DNA which comprises the whole or part of the DNA represented by SEQ ID NO:9 including exons and introns therein, or which consists of a DNA substantially equivalent to one comprising the whole or part of the DNA represented by SEQ ID NO:9 including exons and introns therein.
14. The DNA as claimed in any of the claims 8 to 13, comprising a DNA sequence substantially equivalent to one comprising the whole or part of the DNA represented by SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8 or SEQ ID NO:9, wherein one or more bases have been replaced, deleted and/or

inserted, but still producing an equal effect in gene analysis and diagnosis.

15. A plasmid containing the DNA as claimed in claim 8.
- 5 16. A plasmid containing the DNA as claimed in claim 13.
17. A transformant carrying the plasmid as claimed in claim 15.
18. A transformant carrying the plasmid as claimed in claim 16.
- 10 19. A process for the production of the MDC protein as claimed in claim 1, which comprises the steps of culturing the transformant as claimed in claim 17 and collecting the resulting expression product.
20. A process for the production of the MDC protein as claimed in claim 1, which comprises the steps of
15 culturing the transformant as claimed in claim 18 and collecting the resulting expression product.
21. An antibody combinable to the MDC protein as claimed in claim 1.
22. A primer or probe which has a DNA sequence, comprising a part of the DNA sequence of the DNA as
20 claimed in claim 8, or a DNA sequence complementary to a part of the DNA sequence of the DNA as claimed in claim 8.
23. The primer or probe as claimed in claim 22, wherein the part of the DNA sequence consists of at least
25 six bases.
24. A primer or probe which has a DNA sequence, comprising a part of the DNA sequence of the DNA as
claimed in claim 13, or a DNA sequence complementary to a part of the DNA sequence of the DNA as
claimed in claim 13.
- 30 25. The primer or probe as claimed in claim 24, wherein the part of the DNA sequence consists of at least
six bases.
26. A gene analysis method which comprises the step of hybridizing the primer or probe as claimed in
claim 22 to a DNA to be tested.
- 35 27. A gene analysis method which comprises the step of hybridizing the primer or probe as claimed in
claim 24 to a DNA to be tested.

F I G . 1

13.3	471				453 483 571 586 587 606 624 627 636
13.2	732	488	484 491		645 646 654 657 669 680 685 703 708
13.1		810	525 588		713 716 717 723 727 745 821
12	500 662				
	709 728				
	841				
11.2		681	11 498 502 505 532 536 596 603 608 631 638 688 693		
11.1			694 695 705 712 724 729 802 814 818 825 827 828 832		
11.1			321		
11.1	570 822				
11.2	526 543	32 317 412 425 457 460 468 473 475 482 490 492 497 513 520 562			
	578 602	581 630 640 671 683 698 826 1029 1031 1073 1103 1106 1719 1724			
12	690 801	90 316 535	25 485 552 569 590 599 622 633 637 639 650 687		
	834	583 598 610	706 820 823 1024 1063 1079 1101 1709 1711 1715		
	574	1 57 615	642 673 677	24 415 451 458 463	
21.1		1094 1725		499 506 524 576 601	
21.2				605 1059 1702 1706	
	403				
21.31	1018	28 35 63 96 97 477 479 501 507 517 527 533			
	1705	539 541 542 547 567 582 584 592 609 612 614 617			
21.32	1707	619 634 643 658 670 674 675 701 715 730 736 835			
21.33		1005 1008 1049 1055 1710 1717 1723			
22	7 422 494 515 523 528 611				
	632 652 653 668 1030 1082				
23.1	456	44 50 95 428 618 666	454 462 469 510 530 548 550 553 565 600 604		
23.2	1032	679 711 721 1014 1019	625 626 628 644 655 665 676 678 692 699 700		
23.3	696 743		704 744 809 813 816 817 833 1722 CMM86		
24.1					
24.2		504 509 591			
		667 815			
24.3	464 546				
	559 1720				
25.1			315 465 466 480 493	486 487 514 516 544	
			508 511 521 529 551	554 563 564 572 577	
25.2		469 519	557 560 593 595 621	613 616 641 651 656	
		594 702	623 647 664 672 684	660 663 691 733 739	
25.3	518 549 573 597	722 737	726 742	707 808 831	
	710 714 735 741				

FIG. 2

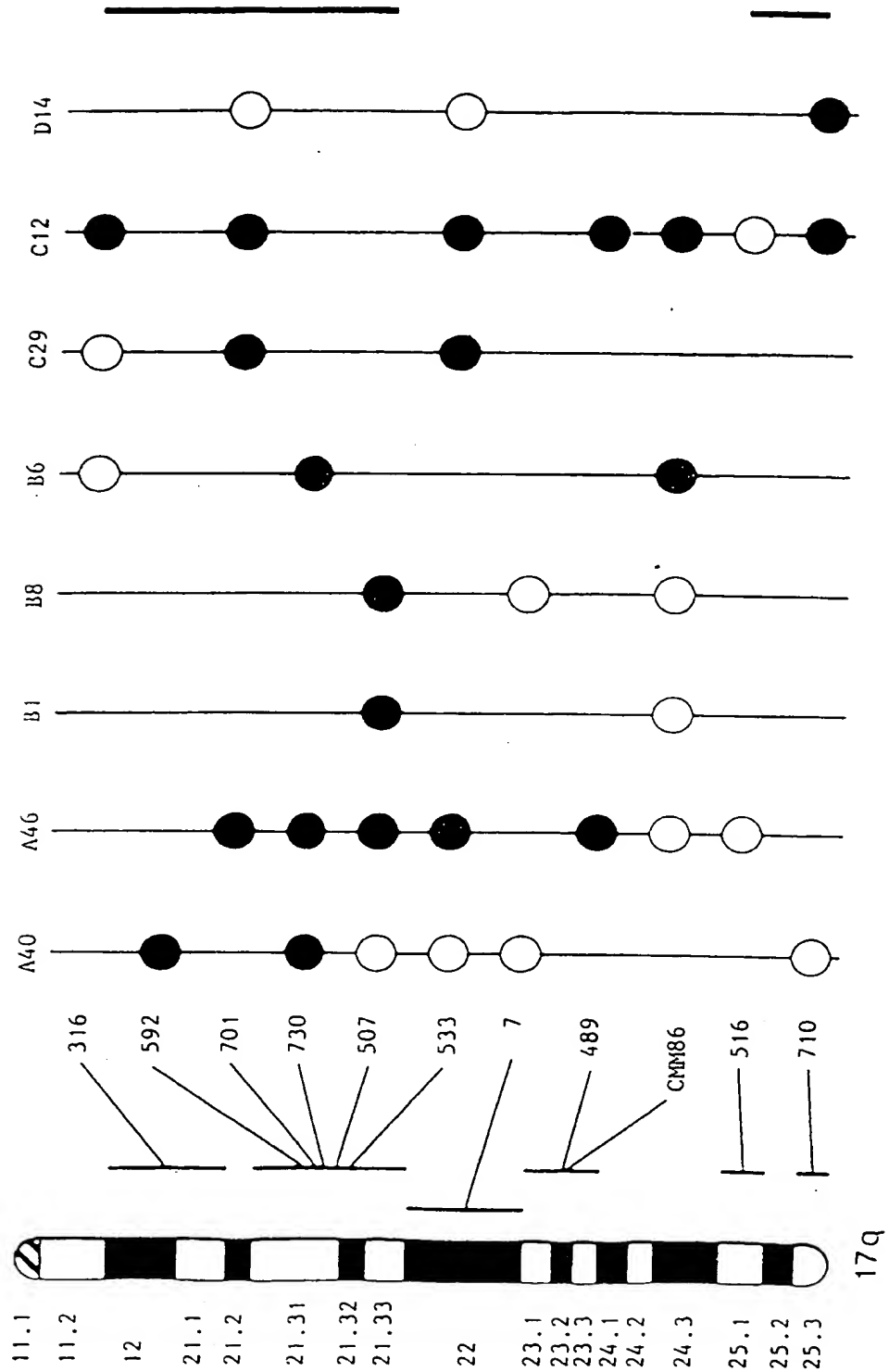
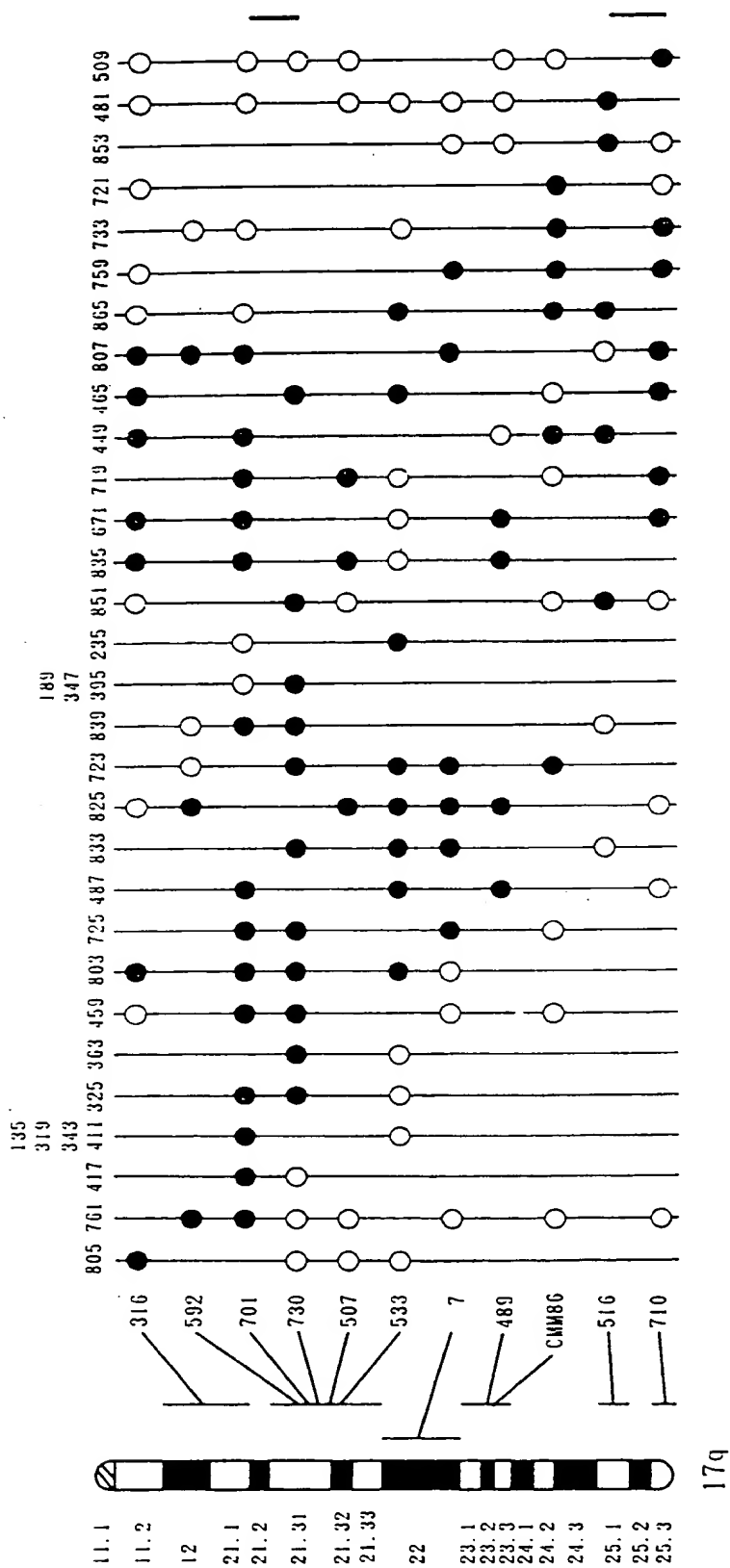


FIG. 3



a

Linkage mapping (<4 cM)

Deletion mapping (2.4 cM)

Tel. Cen.

479	517	730	612	96	28	mfd188	701	PPY		THRA1
541	547		634	675			527	614	592	24
63				617	403		904			35
507	609		674	582	542			670	539	97
658	1008		584	1005	643			736	835	57

Restriction map of the 600/550 kb DNA fragment. The map shows five restriction sites: Mlu I, Sal I, Cla I, and Nru I. The fragment is divided into segments of 280 kb, 300 kb, 220 kb, and 280 kb. Specific features are labeled: mfd188, 904, 527, and 701.

The diagram illustrates the MDC gene structure and experimental strategy. At the top, a cosmid clone (904) is shown with a map of restriction sites (Sal I, Nru I, Cla I) and fragment sizes (2.4, 0.6, 2.2, 9.5, 3.5, 2.6, 0.6, 4.1, 0.1, 1.5, 6.0 kb). Dashed lines indicate the location of MDC cDNA and exons. Below, Tumor 1 and Tumor 2 are shown with shaded regions indicating the presence of the MDC gene. The MDC Exons are numbered 1, 2, 3, 4. Probes are shown at the bottom, including E-H 5.2, A, B, C, D, E, F, and Hind 6.1.

F I G. 5

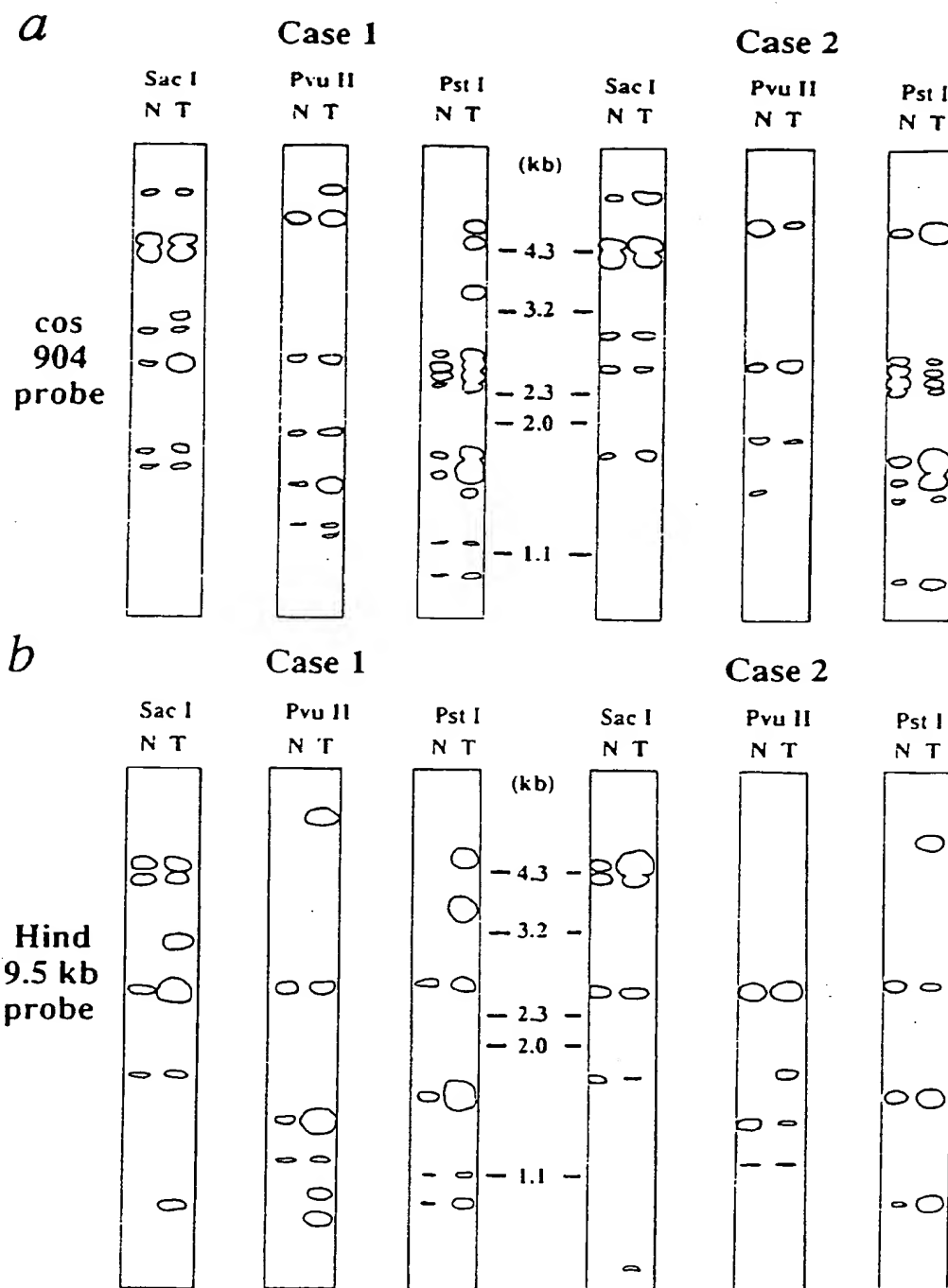


FIG. 6

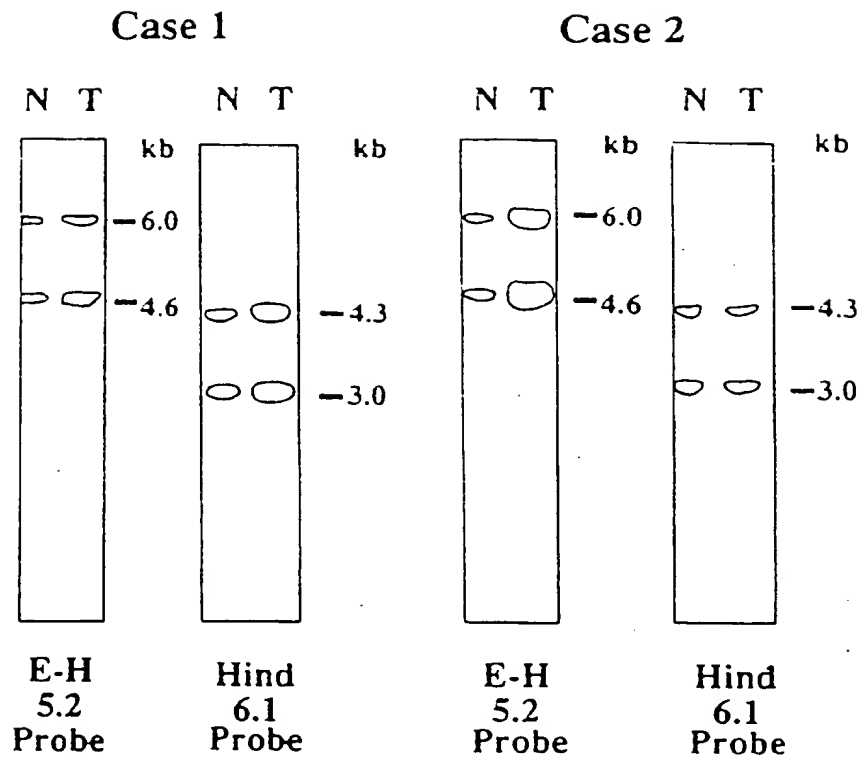
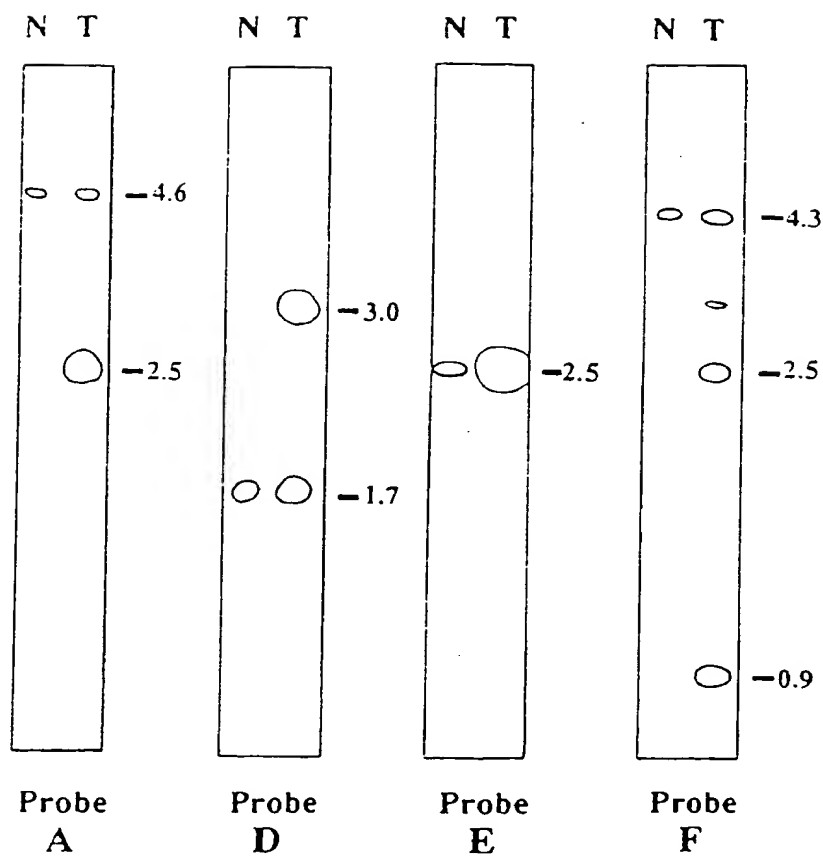
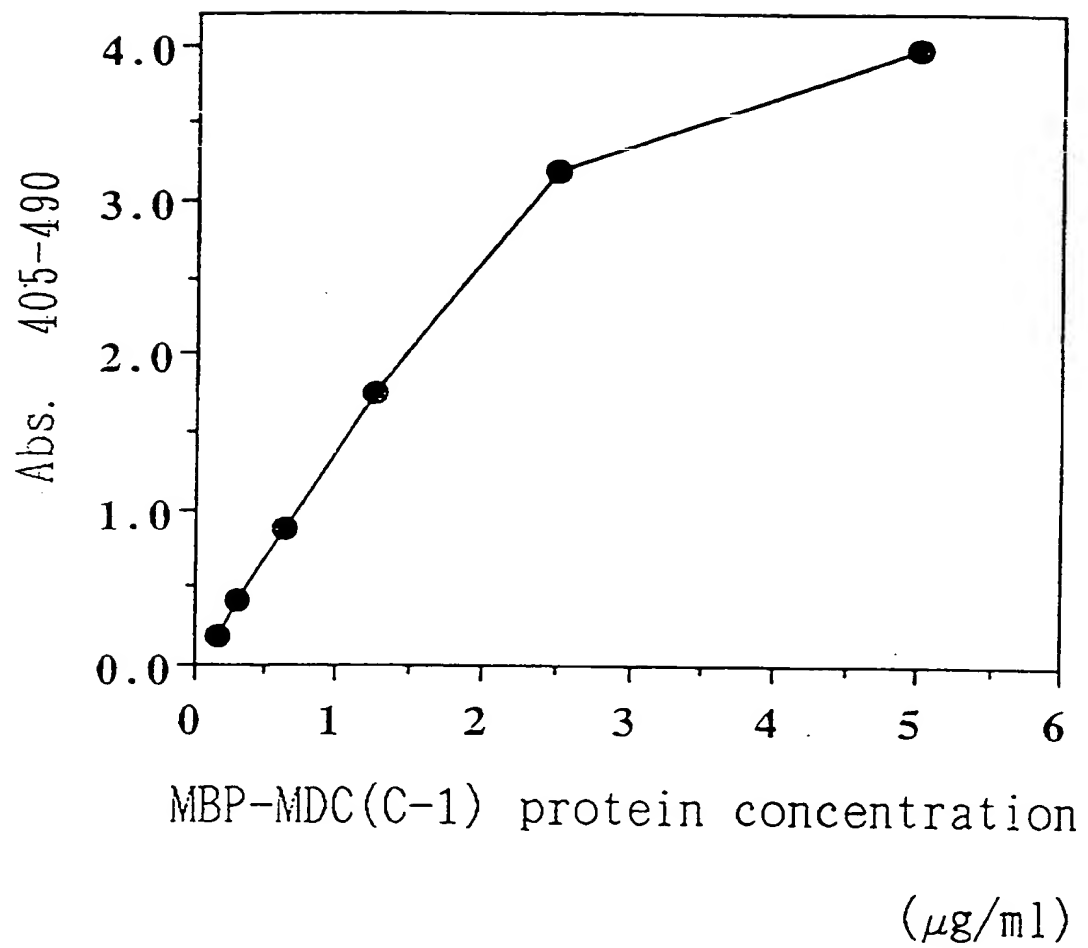


FIG. 7



F I G . 8





(19)



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(54) **MDC proteins and DNAs encoding the same**

(57) The present invention provide a gene present in a commonly deleted region of a chromosome in breast and ovarian cancers and encoding a novel protein, the protein ("MDC protein") encoded by the gene, a method for the diagnosis of cancer by using an antibody combinable to the protein, and others.

A detailed genetic map of human chromosome 17 was constructed to analyze the chromosome in breast and ovarian cancer tissues, and a gene encoding a novel protein was cloned and its structure was determined. As a result of gene analysis using DNA probes derived from the gene, a gene mutation was confirmed in breast cancer tissues. Moreover, a transformant carrying a plasmid containing the gene was grown to obtain the MDC protein. Furthermore, a monoclonal antibody was prepared by using the protein as antigen.

EP 0 633 268 A3



European Patent
Office

EUROPEAN SEARCH REPORT

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EP 94 10 7487

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cls)
X	JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 265, no. 27, 25 September 1990, MD US, pages 16068-16073, XP002036612 H.TAKEYA ET AL.: "The complete amino acid sequence of the high molecular mass hemorrhagic protein HR1B isolated from the venom of Trimeresurus flavoviridis" * figure 2 *	1-7	C07K14/47 C12N15/12 C07K16/18 C12Q1/68 G01N33/574
X	JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 268, no. 2, 15 January 1993, MD US, pages 1058-1065, XP000336706 R.M.SCARBOROUGH ET AL.: "Characterization of the integrin specificities of disintegrins isolated from American pit viper venoms" * table II *	1-7	
A	EP 0 518 650 A (THE JOHN HOPKINS UNIVERSITY; PHARMAGENICS, INC.) 16 December 1992 *SEQ.ID. NO:1 and 2; figure 10a and 10b*	1-27	TECHNICAL FIELDS SEARCHED (Int.Cl.5)
P,X	NATURE GENETICS, vol. 5, no. 2, October 1993, pages 151-157, XP002036047 M.EMI ET AL.: "A novel metalloprotease/disintegrin-like gene at 17q21.3 is somatically rearranged in two primary breast cancers" * the whole document *	1-27	C07K C12N
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 31 July 1997	Examiner Cupido, M
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>			

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EUROPEAN SEARCH REPORT

Application Number
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DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
P, X	<p>CANCER RESEARCH, vol. 53, 15 July 1993, MD US, pages 3382-3385, XP002036048 H.SAITO ET AL.: "Detailed deletion mapping of chromosome 17q in ovarian and breast cancers:2-cM region on 17q21.3 is often and commonly deleted in tumors" * the whole document *</p> <p>-----</p>	8-14	
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The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Examiner	
THE HAGUE	31 July 1997	Cupido, M	
CATEGORY OF CITED DOCUMENTS		<p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons</p> <p>-----</p> <p>& : member of the same patent family, corresponding document</p>	
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